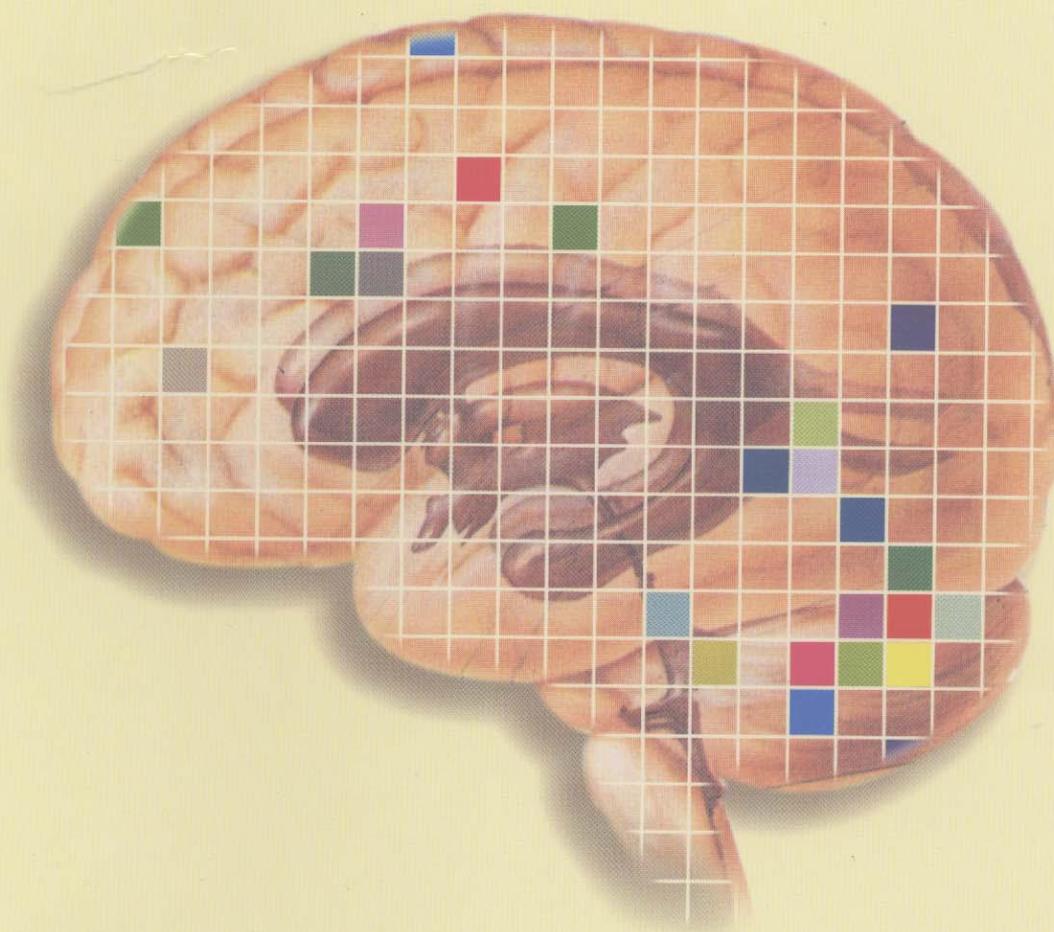


AUTISM SPECTRUM DISORDERS

SELECT ABSTRACTS



INDO-US WORKSHOP

AUTISM SPECTRUM DISORDERS : A CHALLENGING DISABILITY



National Institute for the Mentally Handicapped

AUTISM SPECTRUM DISORDERS SELECT ABSTRACTS

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National Institute for the Mentally Handicapped

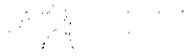
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AUTISM SPECTRUM DISORDERS - SELECT ABSTRACTS (1998-2003)



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18th February 2004

Foreword

Ever since Dr. Leo Kanner described Infantile Autism way back in 1943, the information on this typical conditions has under gone lot of changes. These changes were actually the results of the challenges faced by the professionals in extending services for the children having autism. The transformation from the understanding of autism under Pervasive Developmental Disorder to the refined status of Autism Spectrum Disorder (ASD) has contributed clarity in terms of assessment, diagnosis and management aspects. However, it is refreshing to note that the professionals are into achieving more refined approaches in dealing the children with Autism Spectrum Disorder.

We, at NIMH have always extended support for the professionals in updating with latest information in rehabilitation of persons with mental retardation and associated conditions. We have several models on human resource development and service programmes for persons with mental retardation whereas more evidence based scientific work needs to be done in the area of ASD. As a practised policy of NIMH, we had the opportunity to exchange information with some of the leading institutions in the country and the professionals to take stock of the status of persons with ASD. It was revealing that scientifically designed multidisciplinary services do exist not only for the clients but also for the supporting personnel like parents, siblings and caregivers. During the process, we felt the need for compiling a database on the work done in the area of ASD. The need for this compilation gave us the impetus to bring out - Autism Spectrum Disorder : Select Abstracts. I am glad to present this compiled format of the abstracts it fulfills one of the major objectives of NIMH to document and disseminate information. I hope it will be helpful for all of us to do better in the area of ASD.

Dr. L. Govinda Rao
Director

About this book.....

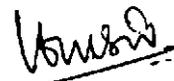
The implementation of the Persons with Disabilities (Equal Opportunities, Protection of Rights and Full Participation) Act, 1995 has made its impact in service delivery, Human Resource Development, Research & Development activities in the area of disability. The Act focuses on the education and employment feasibility for persons with mental retardation. While phenomenal changes have registered in bringing the life of person with mental retardation to be at par with their counter parts, the persons with mental retardation and associated conditions are posing a challenge to the professionals. Autism Spectrum Disorders (ASD) is a group of conditions which require the attention of the multidisciplinary professionals from the area of medical, psychological, special educational and therapeutic specialties. The efforts of the professionals got intensified with the introduction and the implementation of the National Trust for welfare of persons with Autism, Cerebral Palsy, Mental Retardation and Multiple Disabilities Act., 1999.

We at NIMH have been involved in developing service models and human resources required for the services of persons with ASD during the last few years. The need is felt for developing diagnostic, therapeutic and management strategies which are applicable across the cultures. Our recent efforts in bringing the key service providers, researchers and human resource development agencies to one platform gave us the thrust for developing a source of scientific information which can support the strategies being planned to give a dignified life for persons having ASD.

I sincerely present to you a compilation of selected abstracts on the work done in the area of Autism Spectrum Disorders through this book. The scientific information and the research work done in the area was collected from various sources mainly web sources, during the last five years i.e. 1998-2003. These are categorized based on the etiology, course and various management strategies. An effort has been made to present these facts with reference to medical, psychological, educational and therapeutic aspects.

This book is expected to help professionals in their pursuit of seeking explanations for various problems in the field of ASD. However, I would like to mention that this selected list of abstracts can not be considered as an authority for extending services for the persons with Autism Spectrum Disorder. I am glad that this book is being published at a time when NIMH is holding an "Indo-US workshop on Autism Spectrum Disorders: A Challenging Disability" during 10-13 March 2004.

My sincere thanks to our Director, Dr. L. Govinda Rao for his continued support and encouragement in bringing out this book. My heartfelt thanks to Shri T C Sivakumar, Assistant Professor and Head, Department of Adult Independent Living, NIMH, for his moral support and contribution in conceptualization of this book. I would also like to place on record my colleagues Dr PKN Choudary and Dr V Nagaratna for their efforts in compiling the abstracts.



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ETIOLOGY

Medical

1.1.1. Wilson, K., Mills, E., Ross, C., McGowan, J., Jadad, A. "Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: a systematic review of current epidemiological evidence." *Arch Pediatr Adolesc Med.* 2003 Jul;157(7):628-34. Publication Types: Review, Review, Academic.

Department of Medicine and Health Policy, University of Toronto, Ontario, Canada.

OBJECTIVE: To systematically review the evidence for and against the existence of an association between autistic spectrum disorder (ASD) and the measles, mumps, and rubella (MMR) vaccine. **Study DESIGN:** We conducted a systematic review of the medical literature to identify all controlled epidemiological articles examining for an association between ASD and the MMR vaccine. We extracted data from the articles on the characteristics and objectives of the study as well as evidence of an association. **RESULTS:** Twelve articles met the inclusion criteria. One study found no difference in the rates of ASD and the MMR vaccine in children who were vaccinated and those who were not. Six studies examined for evidence of an increase in ASD associated with an increase in the MMR vaccine coverage, none of which showed evidence of an association. Four studies examined if a variant form of ASD was associated with the MMR vaccine, none of which showed evidence of an association. Eight studies attempted to determine if there was a temporal association between developing ASD and receiving the MMR vaccine. Of these, 1 study identified an increase in parental concern in the 6-month period following vaccination with MMR in one of its analyses. The results of all other studies showed no association between ASD and the MMR vaccine. **CONCLUSIONS:** The current literature does not suggest an association between ASD and the MMR vaccine; however, limited epidemiological evidence exists to rule out a link between a rare variant form of ASD and the MMR vaccine. Given the real risks of not vaccinating and that the risks and existence of variant ASD remain theoretical, current policies should continue to advocate the use of the MMR vaccine.

1.1.2. [No authors listed]. "MMR vaccine—how effective and how safe?" *Drug Ther Bull.* 2003 Apr;41(4):25-9.

The introduction of combined measles, mumps and rubella (MMR) vaccine into the UK childhood immunisation schedule in 1988 has markedly reduced the incidence of these diseases and their complications, with, for example, no deaths from acute measles occurring since 1992. However, uptake of MMR vaccine has fallen since the publication, in 1998, of a study that suggested a link between exposure to the vaccine and the development of intestinal inflammation and autism. The study, and the subsequent debate, have attracted considerable media coverage and left many parents and some healthcare professionals uncertain about what to do. While in 1996, 92% of children in England and Wales had received their first dose of the vaccine by the age of 2 years, by 2001-2 this figure had fallen to 84%, with much lower uptake in some regions, threatening a resurgence of all three diseases. Here, we review the evidence for the effectiveness and safety of MMR vaccine.

1.1.3. Miyasaki, M.R., Alejo, R.S., Yamamoto, L.G. "MMR vaccine information on the Internet World Wide Web." *Hawaii Med J.* 2003 Mar;62(3):49-52. Publication Types: Evaluation Studies.

OBJECTIVES: To review world wide web sites that contain information about the MMR vaccine to determine whether the content is accurate compared to recognized standard sources of information. In today's internet age, patients search for information on the internet where there is no regulation of information quality. **METHODS:** By using an internet search engine, several combinations of search terms including "MMR vaccine" were used to find relevant web sites. Sites were classified as favoring MMR use, not favoring MMR use, no position on favoring MMR use. Adverse reactions described in the web site were classified as consistent with, or inconsistent with the adverse reactions described by the standard sources. **RESULTS:** 13% to 40% of web sites favor MMR use depending on the search parameters used. 2.5% to 15% do not favor MMR use. 25% to 63% of the sites took no position on favoring MMR use. 45% to 70% of sites provided "consistent" information on adverse reactions, except for a search using "MMR Vaccine Dangers" which resulted in only 18% of the sites describing "consistent" adverse reaction information. 8% to 38% of sites provided information on adverse reactions which was inconsistent with standard sources, most of which involved information on autism. **CONCLUSIONS:** Most sites do not take a stand on favoring MMR use. Most sites provide adverse reaction information consistent with the standard sources; however, it is likely that parents and patients will encounter sites that provide adverse reaction information, not consistent with standard sources.

1.1.4. Dalton, P., Deacon, R., Blamire, A., Pike, M., McKinlay, I., Stein, J., Styles, P., Vincent, A. "Maternal neuronal antibodies associated with autism and a language disorder." *Ann Neurol.* 2003 Apr;53(4):533-7.

Neurosciences Group, Department of Clinical Neurology, University of Oxford, Oxford, United Kingdom.

Neurodevelopmental disorders could be caused by maternal antibodies or other serum factors. We detected serum antibodies binding to rodent Purkinje cells and other neurons in a mother of three children: the first normal, the second with autism, and the third with a severe specific language disorder. We injected the serum (0.5-1.0 ml/day) into pregnant mice during gestation and found altered exploration and motor coordination and changes in cerebellar magnetic resonance spectroscopy in the mouse offspring, comparing with offspring of mice injected with sera from mothers of healthy children. This evidence supports a role for maternal antibodies in some forms of neurodevelopmental disorder.

1.1.5. Schultz, R.T., Grelotti, D.J., Klin, A., Kleinman, J., Van der Gaag, C., Marois, R., Skudlarski, P. "The role of the fusiform face area in social cognition: implications for the pathobiology of autism." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):415-27.

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A region in the lateral aspect of the fusiform gyrus (FG) is more engaged by human faces than any other category of image. It has come to be known as the 'fusiform face area' (FFA). The origin and extent of this specialization is currently a topic of great interest and debate. This is of special relevance to autism, because recent studies have shown that the FFA is hypoactive to faces in this disorder. In two linked functional magnetic resonance imaging (fMRI) studies of healthy young adults, we show here that the FFA is engaged by a social attribution task (SAT) involving perception of human-like interactions among three simple geometric shapes. The amygdala, temporal pole, medial prefrontal cortex, inferolateral frontal cortex and superior temporal sulci were also significantly engaged. Activation of the FFA to a task without faces challenges the received view that the FFA is restricted in its activities to the perception of faces. We speculate that abstract semantic information associated with faces is encoded in the FG region and retrieved for social computations. From this perspective, the literature on hypoactivation of the FFA in autism may be interpreted as a reflection of a core social cognitive mechanism underlying the disorder.

1.1.6. Hobson, R.P., Bishop, M. "The pathogenesis of autism: insights from congenital blindness." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):335-44.

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There is substantial heterogeneity in the aetiology and clinical presentation of autism. So how do we account for homogeneity in the syndrome? The answer to this question will be critical for any attempt to trace the links between brain pathology and the psychological disabilities that characterize autism. One possibility is that the source of homogeneity in autism is not to be found 'in the child', but rather in dysfunction of the system constituted by child-in-relation-to-other. We have been exploring this hypothesis through the study of congenitally blind children, among whom features of autism, and the syndrome of autism itself, are strikingly common. To justify such an approach, one needs to establish that the clinical features in blind children have qualities that are indeed 'autistic-like'. We conducted systematic observations of the social interactions of two matched groups of congenitally blind children who do not have autism, rating their social engagement, emotional tone, play and language during three sessions of free play in the school playground. The qualities of social impairment in the more disabled children were similar to those in sighted children with autism. Additional evidence came from independent ratings of the children in a different play setting: on the childhood autism rating scale (CARS), the socially impaired children had 'autistic-like' abnormalities in both social and non-social domains. If we can determine the way in which congenital blindness predisposes to features of autism, we shall be in a better position to trace the developmental pathways that lead to the syndrome in sighted children.

1.1.7. Teitelbaum, P. "A proposed primate animal model of autism." *Eur Child Adolesc Psychiatry.* 2003 Jan;12(1):48-9. Publication Types: Letter.

Based on the fact that thalidomide, at a certain point in human pregnancy, produces autism, we propose administering thalidomide to pregnant monkeys at an appropriate point after conception. The infant monkeys born after thalidomide treatment of the pregnant mothers should manifest aberrations in social vocalization and in socialization behavior. Histological analysis of their brains should reveal areas whose damage will lead to autism. This can then be produced stereotaxically in infant monkeys to allow the better determination of the relation of degree of damage in these areas to the severity of autism.

1.1.8. Chen, D.T., Miller, F.G., Rosenstein, D.L. "Ethical aspects of research into the etiology of autism." *Ment Retard Dev Disabil Res Rev.* 2003;9(1):48-53. Publication Types: Review, Review, Tutorial.

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Advances in understanding autism and other developmental neuropsychiatric disorders will come from an integration of various research strategies including phenomenologic, functional neuroimaging, and pharmacologic methods, as well as epidemiologic approaches aimed at identifying genetic and environmental risk factors. The highly heritable nature of autism makes it scientifically valuable to involve parents and siblings as research participants. However, many studies on autism pose ethical challenges because they do not offer the prospect of direct benefit to subjects. In this article, we present an in-depth ethical analysis of current nontherapeutic research strategies that are common in autism research. The ethical analysis applies a proposed ethical framework for evaluating clinical research focusing on seven ethical requirements: (1) social or scientific value, (2) scientific validity, (3) fair subject selection, (4) favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for potential and enrolled research participants. Copyright 2003 Wiley-Liss, Inc. MRDD Research Reviews 2003;9:48-53.

1.1.9. Acosta, M.T., Pearl, P.L. "The neurobiology of autism: new pieces of the puzzle." *Curr Neurol Neurosci Rep.* 2003 Mar;3(2):149-56. Publication Types: Review, Review, Tutorial.

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The neurobiologic basis of autism is reviewed, with discussion of evidence from genetic, magnetic resonance imaging, neuropathology, and functional neuroimaging studies. Although autism is a behaviorally valid syndrome, it is remarkably heterogeneous and involves multiple developmental domains as well as a wide range of cognitive, language, and socioemotional functioning. Although multiple etiologies are implicated, recent advances have identified common themes in pathophysiology. Genetic factors play a

primary role, based on evidence from family studies, identification of putative genes using genome-wide linkage analyses, and comorbidities with known genetic mutations. The RELN gene, which codes for an extracellular protein guiding neuronal migration, has been implicated in autism. Numerous neuropathologic changes have been described, including macroencephaly, acceleration and then deceleration in brain growth, increased neuronal packing and decreased cell size in the limbic system, and decreased Purkinje cell number in the cerebellum. Abnormalities in organization of the cortical minicolumn, representing the fundamental subunit of vertical cortical organization, may underlie the pathology of autism and result in altered thalamocortical connections, cortical disinhibition, and dysfunction of the arousal-modulating system of the brain. The role of acquired factors is speculative, with insufficient evidence to link the measles-mumps-rubella (MMR) vaccine with autism or to change immunization practices.

1.1.10. DeStefano, F., Thompson, W.W. "MMR vaccination and autism: is there a link?" *Expert Opin Drug Saf.* 2002 Jul;1(2):115-20. Publication Types: Editorial, Review, Review Tutorial.

In 1998, a report was published describing 12 patients with inflammatory bowel conditions and regressive developmental disorders consisting primarily of autism. The authors hypothesized that MMR vaccine may have been responsible for the bowel dysfunction which subsequently resulted in the neurodevelopmental disorders. The suggestion that measles vaccine may cause autism through a persistent bowel infection generated much interest since it provided a possible biological mechanism for a causal association. Epidemiological studies, however, have not found an association between MMR vaccination and autism. Autism has a strong genetic component and its associated neurological defects probably occur during embryonic development. It seems unlikely that a vaccination that is given after birth could cause autism. In a minority of cases, autism may have onset after 1 year of age (regressive autism) but the one epidemiological study that included such cases did not find an association with MMR vaccination. Currently, the weight of the available epidemiological and related evidence does not support a causal link between MMR vaccine and autism.

1.1.11. Coffin, S.E. "MMR and autism: moving from controversy toward consensus." *Expert Rev Vaccines.* 2002 Aug;1(2):145-50. Publication Types: Review, Tutorial.

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As controversy swirls around the putative association between the measles-mumps-rubella vaccine and autism, the methods of scientific investigation, established more than 150 years ago, bear remembering. In this article, we will discuss the origins of this hypothesis, evidence in support of and at variance with this theory and future investigations that may help to resolve this debate.

1.1.12. Wilkerson, D.S., Volpe, A.G., Dean, R.S., Titus, J.B. "Perinatal complications as predictors of infantile autism." *Int J Neurosci.* 2002 Sep;112(9):1085-98.

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This study investigated the relationship between reported perinatal complications and autism. The biological mothers of 183 autistic children and 209 normals completed the Maternal Perinatal Scale (MPS), a maternal self-report that surveys complications of pregnancies and medical conditions of the mother. Previous research in this area has been limited, with no definitive conclusions. A discriminant analysis was performed to consider perinatal complications as predictors between the autistic and normal subjects. Using the MPS, 65% of the autistic cases were correctly grouped. The results further indicated significant differences on 3 of the 10 factors of the MPS, in particular, Gestational Age, Maternal Morphology, and Intrauterine Stress. When considered in an item by item fashion, 5 items were found to significantly predict group membership (prescriptions taken during pregnancy, length of labor, viral infection, abnormal presentation at delivery, and low birth weight). Finally, 3 maternal medical conditions were found to be highly significant and contribute to the separation between groups, including urinary infection, high temperatures, and depression.

1.1.13. Akshoomoff, N., Pierce, K., Courchesne, E. "The neurobiological basis of autism from a developmental perspective." *Dev Psychopathol* 2002 Summer; 14(3):613-34. Publication Types: Review, Review, Academic.

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Autism is a neurobiological disorder that is diagnosed through careful behavioral assessment in early childhood. In this paper, we review recent studies that have attempted to reveal the underlying causes of autism using a variety of techniques. Particular emphasis is placed on techniques that have been used by a number of different laboratories, including structural magnetic resonance imaging and postmortem studies of neuroanatomy. Neurobiological and neuropsychological data from individuals across a wide age range are examined from a neurodevelopmental perspective. We discuss how these recent advances have led us to develop a growth dysregulation hypothesis of autism. Finally, we discuss how this hypothesis may lead to new innovations in autism research.

1.1.14. Rodier, P.M. "Converging evidence for brain stem injury in autism." *Dev Psychopathol* 2002 Summer;14(3):537-57.

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The hypothesis that brain stem injury plays a role in the autism spectrum disorders was suggested by evidence that exposure to thalidomide during the earliest stages of brain development increases the risk of autism spectrum disorders. The implications for the embryological origin of autism first led

to studies of neuroanatomy in a human case and an animal model and then to examinations of minor craniofacial features in autism. But the general hypothesis had much broader implications. It has now generated studies of the behavioral and neurological symptoms of human patients, of human molecular genetics and population genetics, and of animal behavioral teratology and molecular pharmacology. The collection of this range of data was made possible by adding experts from many fields to the research team. They worked both independently and collaboratively to try to unravel the etiology of autism.

1.1.15. Elliman, D.A., Bedford, H.E. "Measles, mumps and rubella vaccine, autism and inflammatory bowel disease: advising concerned parents." *Paediatr Drugs* 2002;4(10):631-5. Publication Types: Review, Review, Tutorial.

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Measles, mumps and rubella (MMR) vaccine has been used for almost 30 years in the US, 20 years in Sweden and Finland, and over 10 years in most of the rest of Europe. During this time, it has brought about a dramatic reduction in the morbidity and mortality due to measles and mumps, as well as a considerable reduction in the number of babies with the congenital rubella syndrome. In spite of extensive evidence confirming the efficacy and safety of the vaccine, concerns have recently been raised about a possible link with autism and bowel problems. These arose principally from a research group in the UK, but have now spread to other countries. In the UK this has caused a fall in the uptake of the vaccine with fears of possible outbreaks of measles and mumps in some groups of children. Over the last 3 years a number of studies have addressed this possible link between MMR and autism and inflammatory bowel disease. Studies from the US, UK, Sweden, and Finland have all failed to demonstrate a link. Amongst others, the American Academy of Pediatrics, the Royal College of Paediatrics and Child Health, the Institute of Medicine, and the World Health Organization have all considered the evidence and endorsed the continuing use of the vaccine. No regulatory body in the world has changed its policy as a result of this hypothesized link. Professionals and parents can be assured that MMR is well tried and tested and one of the most successful interventions in healthcare.

1.1.16. Devlin, B., Bennett, P., Cook, E.H. Jr., Dawson, G., Gonen, D., Grigorenko, E.L., McMahon, W., Pauls, D., Smith, M., Spence, M.A., Schellenberg, G.D. "No evidence for linkage of liability to autism to HOXA1 in a sample from the CPEA network." *Am J Med Genet* 2002 Aug 8;114(6):667-72. Publication Types: Multicenter Study.

CPEA Genetics Network. Collaborative Programs of Excellence in Autism.

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A recent study by Ingram et al. [2000b: *Teratology* 62:393-405] suggests a (His)73(Arg) polymorphism (A:G) in HOXA1 contributes substantially to a liability for autism. Using 68

individuals diagnosed with Autism Spectrum Disorders, they found a significant dearth of G homozygotes and biased transmission of G alleles from parents to affected offspring, especially from mothers. Because the connection between HOXA1 and liability to autism is compelling, we attempted to replicate their finding using a larger, independent sample from the Collaborative Programs of Excellence in Autism (CPEA) network. In our data, genotype frequencies conform to Hardy-Weinberg equilibrium; allele transmissions meet Mendelian expectations; and there is no obvious sex-biased allele transmission. Based on our sample size, calculations suggest that we would have at least 95% power to detect linkage and association even if the A:G polymorphism were to account for only 1% of the heritability of autism. Therefore, although we cannot exclude the possibility that the samples in the two studies are intrinsically different, our data from our sample argue against a major role for HOXA1 (His)73(Arg) in liability to autism. Copyright 2002 Wiley-Liss, Inc.

1.1.17. Yazbak, F.E., Yazbak, K. "Live virus vaccination near a pregnancy: flawed policies, tragic results." *Med Hypotheses* 2002 Sep;59(3):283-8. Publication Types: Review, Review, Tutorial.

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Vaccination of women with live virus vaccines around conception has always been contraindicated by the Center for Disease Control and Prevention (CDC) and the vaccine manufacturer because of potential risks to the fetus. Nevertheless this dangerous practice occurs and is associated with maternal health problems and a very high incidence of early-onset autism in the children. Postpartum vaccination with live virus vaccines has been recommended by the CDC, and described as 'convenient' by the vaccine manufacturer. This 'routine practice' may lead to health and is also associated with many health and obstetrical problems in the recipient, and is frequently associated with autism in both current and future children. Re-vaccination often fails to produce immunity, the very reason for which it was recommended.

1.1.18. Halsey, N.A. "The science of evaluation of adverse events associated with vaccination." *Semin Pediatr Infect Dis* 2002 Jul;13(3):205-14. Publication Types: Review, Review, Tutorial.

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All vaccines cause some adverse events; serious adverse events are rare. Causal associations between a vaccine and an adverse event rarely can be determined by specific tests such as identifying a vaccine agent in the affected tissue of patients. In the absence of such data, epidemiologic studies can be used to determine if the risk of the disorder is increased in vaccinated compared to unvaccinated individuals. Common mistakes include assuming a causal relationship based on a temporal association only or a series of affected patients. Careful studies have demonstrated that many hypothesized

causal associations between vaccines and adverse events were not substantiated. False assumptions regarding causality are likely to occur for illnesses without a carefully defined etiology or pathogenesis.

1.1.19. Krause, I., He, X.S., Gershwin, M.E., Shoenfeld, Y.J., "Brief report: immune factors in autism: a critical review." *Autism Dev Disord* 2002 Aug;32(4):337-45. Publication Types: Review, Review, Academic.

Research Unit of Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, and the Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Pervasive developmental disorders represent a group of neurodevelopmental disorders that affect children early in their development. Autistic disorder is the best described of these disorders, yet even this term covers a broad group of clinical presentations. Various immune system abnormalities, including autoimmunity and defects in different subsets of immune cells, have been reported in children with autistic disorder, suggesting that immune factors may play a role in the development of autism. Based on anecdotal observation, vaccination was proposed to cause autism in some children, but several controlled studies have failed to support this claim. Intravenous immunoglobulin infusions has been tested as immunotherapy for autism, although the preliminary results are inconclusive and there is a risk of potentially fatal transmission of blood-borne pathogens. To examine this issue, intensive well-controlled epidemiological and bench studies need to be carried out in defined and carefully controlled study subjects to establish the cellular and molecular basis of autism, against which the effects of each proposed immune factor can be examined.

1.1.20. Hultman, C.M., Sparen, P., Cnattingius, S. "Perinatal risk factors for infantile autism." *Epidemiology* 2002 Jul;13(4):417-23.

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BACKGROUND: Etiologic hypotheses in infantile autism suggest a strong genetic component, as well as possible environmental risks linked to early fetal development. We evaluated the association of maternal, pregnancy, delivery, and infant characteristics and risk of infantile autism. **METHODS:** We conducted a case-control study nested within a population-based cohort (all Swedish children born in 1974-1993). We used prospectively recorded data from the Swedish Birth Register, which were individually linked to the Swedish Inpatient Register. Cases were 408 children (321 boys and 87 girls) discharged with a main diagnosis of infantile autism from any hospital in Sweden before 10 years of age in the period 1987-1994, plus 2,040 matched controls. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). **RESULTS:** The risk of autism was associated with daily smoking in early pregnancy (OR = 1.4; CI = 1.1-1.8), maternal birth outside Europe and North America (OR = 3.0; CI = 1.7-5.2), cesarean delivery (OR = 1.6; CI = 1.1-2.3), being small for gestational age (SGA; OR

= 2.1; CI = 1.1-3.9), a 5-minute Apgar score below 7 (OR = 3.2, CI = 1.2-8.2), and congenital malformations (OR = 1.8, CI = 1.1-3.1). No association was found between autism and head circumference, maternal diabetes, being a twin, or season of birth. **CONCLUSIONS:** Our findings suggest that intrauterine and neonatal factors related to deviant intrauterine growth or fetal distress are important in the pathogenesis of autism.

1.1.21. Lauritsen, M.B., Mors, O., Mortensen, P.B., Ewald, H.J. "Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study." *Autism Dev Disord* 2002 Apr;32(2):115-9.

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Possible associations between autism and specific medical disorders have been suggested, and this could be of relevance in the clinical examination and treatment of patients and may help to identify factors involved in the etiology or pathophysiology of autism. Two population-based Danish registers were used to investigate the occurrence of medical disorders in patients with autism according to ICD-8 and in a matched control sample. A total of 29 of the 244 patients (11.9%) diagnosed with autism had one or more medical disorders. In contrast to previous studies, we did not find an increased occurrence of almost any medical disorders. A highly significant increased frequency of congenital malformations was found, which may indicate abnormalities in embryogenesis in the etiology of autism.

1.1.22. Evans, M., Stoddart, H., Condon, L., Freeman, E., Grizzell, M., Mullen, R. "Comment in: Parents' perspectives on the MMR immunisation: a focus group study." *Br J Gen Pract* 2001 Nov; 51 (472): 904-10.

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BACKGROUND: The uptake of the combined measles, mumps and rubella immunisation (MMR) in Britain has fallen since 1998, when a link was hypothesised with the Development of bowel disorders and childhood autism. Despite reassurances about the safety of MMR, uptake levels remain lower than optimal. We need to understand what influences parents' decisions on whether to accept MMR or not so that health professionals can provide a service responsive to their needs. **AIM :** To investigate what influences parents' decisions on whether to accept or refuse the primary MMR immunisation and the impact of the recent controversy over its safety. **DESIGN :** Qualitative study using focus group discussions. **SETTING :** Forty- eight parents, whose youngest child was between 14 months and three years old, attended groups at community halls in six localities in Avon and Gloucestershire. **METHODS:** Purposive sampling strategy was used to include parents from a variety of socioeconomic backgrounds. Three groups comprised parents who had accepted MMR and three groups comprised parents who had refused MMR. Data analysis used modified grounded theory techniques incorporating the constant

comparative method. **RESULTS** : All parents felt that the decision about MMR was difficult and stressful, and experienced unwelcome pressure from health professionals to comply. Parents were not convinced by Department of Health reassurance that MMR was the safest and the best option for their children and many had accepted MMR unwillingly. Four key factors influenced parents' decision : (a) beliefs about the risks and benefits of MMR compared with contracting the diseases, (b) Information from the media and other sources about the safety of MMR, (c) confidence and trust in the advice of health professionals and attitudes towards compliance with this advice, and (d) views on the importance of individual choice within Government policy on immunisation. **CONCLUSIONS** : Parents wanted up-to-date information about the risks and benefits of MMR to be available in advance of their immunisation appointment. Many parents did not have confidence in the recommendations of health professionals because they were aware that GPs needed to reach immunisation targets. Most parents would, however, welcome more open discussion about immunisation with health professionals.

1.1.23. Whitaker - Azmitia, P.M. "**Serotonin and brain development role in human developmental diseases.**" *Brain Res Bull* 2001 Nov 15;56(5) : 479-85. Publication Types: Review, Review, Academic.

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Serotonin is known to play a role in brain development prior to the time it assumes its role as a neurotransmitter in the mature brain. Serotonin regulates both the development of serotonergic neurons (termed autoregulation of development) and the development of target tissues. In both cases, the astroglial-derived protein, S-100beta plays a role. Disruption of serotonergic development can leave permanent alterations in brain function and behaviour. This may be the case in such human developmental illness as autism and Down Syndrome.

1.1.24. Okado, N., Narita, M., Narita, N. "**A biogenic amine - synapse mechanism for mental retardation and developmental disabilities.**" *Brain Dev* 2001 Dec;23 Suppl 1: S11-5. Publication Types: Review, Review, Tutorial.

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Recent studies have demonstrated that biogenic amines have a function of facilitating formation and maintenance of synapses in diverse regions of the central nervous system in developing and adult animals. The normal number of synapses maintained by biogenic amines are crucial to acquire learning and memory. The level of biogenic amines was reported to decrease in the brain by several neurodevelopmental disorders associated with mental retardation and developmental disabilities such as Rett syndrome, autism and Down Syndrome. Taken into consideration this fact together with the function of biogenic amines for synapses, the density

of synapses appears to decrease considerably in the brains of patients suffered from the neurodevelopmental disorders. The synaptic over production during the critical period of development especially 1 year after birth as been considered as a background mechanism to provide plasticity for the developing brain. Synaptic over production does not appear to occur in the brains of patients suffered from the neurodevelopmental disorders, which they are observed mental retardation occurring in the first 1 year after birth. Along with the neurodevelopmental disorders, environmental factors (stress, drugs and nutrition) during pre- and post-natal critical developmental periods are known to change levels of biogenic amines in the brain. In fact, maternal stress has been shown to decrease the level of serotonin and the density of synapses in the spatial learning and memory. A cascade appears to exist from either the child neurological disorders or the environmental factors to mental retardation and developmental disabilities by decreases in the levels of biogenic amines and synaptic density.

1.1.25. Azmitia, E.C. "**Neuronal instability : implications for Rett's syndrome.**" *Brain Dev* 2001 Dec; 23 Suppl 1: S1 - S10. Publication Types: Review, Review, Tutorial.

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The maturational changes in the brain and spinal cord do not linearly proceed from immature in infants to mature in adults. Dendrites dynamically extend or retract as neurotrophic factors fluctuate. In certain cases mature neurons can be seen soon after birth, and in other cases immature neurons can be aged brain. Monoamine 'neurotransmitter' ; such as serotonin (5-HT), dopamine and norepinephrine appear to function as Maintenance Growth Factors since they must be present in order to produce their maturational actions. Serotonin neurons contain TRK IB receptors and are sensitive to availability of the trophic factor, BDNF. 5-HT also functions by promoting the release of the glial extension factor, S-100beta. 5-HT and S-100 beta and provide maturational signals to a variety of neurons, in both cortical and subcortical areas, and appear to be involved in regulating the maturation and release of acetylcholine and dopamine. We have shown that activation of the 5- HT1A receptor is particularly effective in inducing growth of stunted neurons. The Mechanism of action of the 5- HT1A receptor involves both a direct inhibition on c-AMP AND PKC formation in postsynaptic neurons and a release of S- 100 beta from glial cells. Both these events are capable of stabilization and elaboration of the cytoskeleton of the neuron and inhibition of apoptosis. 5- HT1A agonists in children with developmental disorders.

1.1.26. Weideneim, K.M., Goodman, L.; Dickson, D.W., Gillberg, C., Rastam, M., Rapin, I. "**Etiology and pathophysiology of autistic behaviour : clues from two cases with an unusual variant of neuroaxonal dystrophy.**" *J Child Neurol* 2001 Nov; 16(11) : 809-19.

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Two unrelated individuals with autistic behaviour had numerous swollen axon terminals (spheroids) located in specific brain regions relevant to their behavioural symptoms. Spheroids are characteristic of neuroaxonal dystrophy, but the clinical profile and anatomic distribution of the lesions in these two patients differed from those of previously described patients with neuroaxonal dystrophy. Spheroids were numerous in the sensory nuclei of the spinal cord and medulla, specific nuclei and the reticular formation of the brainstem tegmentum, hypothalamus, anterior and dorsomedial thalamus, hippocampus, and cingulate and orbitofrontal cortices. Spheroids were sparse in the primary and association cortices and basal ganglia and absent in the hemispheric white matter. Cerebellar trophic was present in both cases but associated with spheroids in only one case. These cases represent a new variant of neuroaxonal dystrophy in which behavioural symptoms characteristic of autism dominated the clinical picture. Neuroaxonal dystrophy should be included in the list of diseases that may be found in persons with autism.

1.1.27. Fatemi, S.H., Kroll, J.L., Stary, J.M. "Altered levels of Reelin and its isoforms in schizophrenia and mood disorders." *Neuroreport* 2001 Oct 29; 12(15): 3209-15. PMID 11711858

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Reelin is a secreted extracellular matrix protein approximately 410 kDa mol. wt that is reduced in brains of patients with schizophrenia, autism, bipolar disorder and major depression. Recent reports also indicate its near absence in sera of some patients with an autosomal recessive form of lissencephaly. Moreover, Reelin is involved not only in normal cortical lamination of the brain during mammalian embryogenesis but is also implicated in cell signaling systems subserving cognition in adult brain. Here, we show that blood levels of Reelin and its isoforms are altered in three psychiatric disorders, namely, schizophrenia, bipolar disorder and major depression. The changes include significant increases in 410 kDa Reelin moiety of 49% in schizophrenic patients ($p < 0.022$) of four ethnic compositions (Caucasian, Vietnamese, Hmong and Laotian) and non-significant increases in depressed patients by 34% vs control blood. In contrast 410kDa Reelin levels decreased by 33% in bipolar blood, albeit non-significantly, vs controls. There was a significant increase of 90% ($p < 0.0061$) in 330kDa Reelin in Caucasian schizophrenics, the depressed value was elevated by 30% vs. Control but non-significantly. Again, in contrast, the 180kDa Reelin values dropped significantly by 49% ($p < 0.00117$) and 29% ($p < 0.0424$) in bipolar and depressed patients, respectively, compared with controls. The alterations in blood Reelin values appear to be specific since levels of two other blood Reelin levels and its isoforms may be used as potential peripheral markers to diagnose presence of several Psychiatric disorders and may also serve as targets for future therapeutic interventions.

1.1.28. DeStefano, F., Chen, R.T "Autism and measles - mumps - rubella vaccination : controversy laid to rest?" *CNS Drugs* 2001; 15(11) :831-7. Publication Types: Review, Review Tutorial.

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It has been suggested that vaccination, particularly with measles-mumps - rubella (MMR) vaccine, may be related to the development of autism. The main evidence for a possible association is that the prevalence of autism has been increasing at the same time that infant vaccination coverage has increased, and that in some cases there is an apparent temporal association in which autistic characteristics are first noted shortly after vaccination. Although the prevalence of autism and similar disorder appears to have increased recently, it is not clear if this is an actual increase or the result of increased recognition and changes in diagnostic criteria. The apparent onset of autism in close proximity to vaccination may be a coincidental temporal association. The clinical evidence in support of an association derives from a series of 12 patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism. The possibility that measles vaccine may cause autism through a persistent bowel infection has generated much interest, since it provides a possible biological mechanism. Epidemiological studies, however, have not found an association between MMR vaccination and autism. The epidemiological findings are consistent with current understanding of the pathogenesis of autism, which has a strong genetic component and in which the neurological defects probably occur early in embryonic development. It seems unlikely that a vaccination that is given after birth could cause autism. A minority of cases of autism may have onset after 1 such cases did not find an association with MMR vaccination. Currently, the weight of the available epidemiological and related evidence does not support a causal association between MMR vaccine, or any other vaccine or vaccine constituent, and autism.

1.1.29. Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., Morris, M. "Oxytocin and autistic disorder : alterations in peptide forms." *Bio Psychiatry* 2001 Oct 15; 50(8) : 609-13.

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BACKGROUND . Oxytocin (OT) is synthesized as a prohormone is sequentially processed to peptides. These peptides are the bioactive amidated form (OT) and the C-terminal extended peptides, OT-Gly, OTY-Gly-Lys and OT-Gly-Lys-Arg, which are designated together as OT-X. As an extension of our previous study finding decreased plasma OT peptide forms in autistic children **METHODS**: Twenty eight male subjects (97+/-20months, range, 70- 139months), diagnosed with DSM-IV autistic disorder through observation and semi-structured interview, were compared with 31 age-matched nonpsychiatric control subjects (106+/-22 months; range 74-140 months). Using OT antisera with different

specificity for the peptide forms, we measured plasma OT and OT-X in each group RESULTS : T tests showed that there was a decrease in plasma OT ($t = 4.4, p < 0001$), an increase in OT-X ($t = 2.3, p < .03$) and an increase in the ratio of OT-X/OT ($t = 4.5, p < 0001$) in the autistic sample, compared with control subjects CONCLUSIONS: The results suggest that children with autistic disorder show alterations in the endocrine OT system. Deficits in OT peptide processing in children with autism may be important in the development of this syndrome.

1.1.30. Asano, E., Chugani, D.C., Muzik, O., Behen, M., Janisse, J., Rothermel, R., Mangner, T.J., Chakraborty, P.K., Chugani, H.T. "Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction." *Neurology* 2001 Oct 9;57(7) : 1269-77.

Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit 48201, USA.

OBJECTIVE : To examine the relationship between autism and epilepsy in relation to structural and functional brain abnormalities in children with tuberous sclerosis complex (TSC). METHODS : Children with TSC and intractable epilepsy underwent MRI as well as PET scans with 2-deoxy-2-[(18)F] fluoro-D-glucose (FDB) as alpha-[(11)C] methyl-L-tryptophan (AMT). Based on the results of Autism Diagnostic Interview-Revised, Gilliam Autism Rating Scale, and overall adaptive behavioral composite (OABC) from Vineland Adaptive Behavior Scale, subjects were divided into three groups: autistic (OABC < 70; n=9), mentally -retarded nonautistic (OABC > 70; n=9), and relatively normal intelligence (OABC < or = 70; n=8). RESULTS : PET studies showed that the autistic group had decreased glucose metabolism in the lateral temporal gyri bilaterally, increased glucose metabolism in the deep cerebellar nuclei bilaterally, and increased AMT uptake in the caudate nuclei bilaterally, compared to the mentally-retarded nonautistic group. In addition, a history of infantile spasms and glucose hypometabolism in the lateral temporal gyri were both significantly associated with communication disturbance. Glucose hypermetabolism in the deep cerebellar nuclei and increased AMT uptake in the caudate nuclei were both related to stereotypical behaviors and impaired social interaction, as well as communication disturbance. CONCLUSIONS : These results suggest that generalized epilepsy in early life and functional deficits in the temporal neocortex may be associated with communication delays, and that functional imbalance in subcortical circuits may be associated with stereotypical behaviors and impaired social interaction in children with TSC.

1.1.31. Pearce, C.B., Martin, H., Duncan, H.D., Goggin, P.M., Poller, D.N. "Colonic lymphoid hyperplasia in melanosis coli." *Arch Pathol Lab Med* 2001 Aug;125(8):1110-2.

Queen Alexandra Hospital, Portsmouth PO6 3LY, United Kingdom.

We describe the case of a patient with Rett syndrome, a syndrome characterized by progressive infant encephalopathy, developmental delay, dementia, autism,

ataxia, microcephaly, spastic paraparesis, and autonomic neuropathy with constipation. At colonoscopy, multiple foci of tiny white, sessile, polypoid lesions were seen throughout the colon and rectum, mimicking the appearances of small hyperplastic or adenomatous polyps, associated with generalized melanosis coli. This is the first case to our knowledge describing melanosis coli in a patient with Rett syndrome. As melanosis pigment deposition is characteristically not seen in lymphoid tissue, the lymphoid tissue was identifiable at endoscopy as multiple white nodules mimicking generalized colonic polyposis throughout the colon. We discuss the likely mechanisms of lymphoid hyperplasia and coexistent melanosis coli in Rett syndrome.

1.1.32. Perry, E.K., Lee, M.L., Martin-Ruiz, C.M., Court, J.A., Volsen, S.G., Merrit, J., Folly, E., Iversen, P.E., Bauman, M.L., Perry, R.H., Wenk, G.L. "Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain." *Am J Psychiatry* 2001 Jul;158(7):1058-66.

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OBJECTIVE: Measures of cholinergic transmitter activity were investigated in patients with autism because of reported neuropathological abnormalities in cholinergic nuclei in the basal forebrain. METHOD: Levels of cholinergic enzyme and receptor activity were measured in the frontal and parietal cerebral cortex of deceased autistic adults, similarly aged normal adults without mental retardation, and nonautistic mentally retarded adults. The immunoreactivity levels of brain-derived neurotrophic factor and nerve growth factor were measured in the basal forebrain. RESULTS: There were no differences between the autistic and comparison groups in choline acetyltransferase or acetylcholinesterase activity in the cerebral cortex and basal forebrain or in muscarinic M(2) receptor or alpha-bungarotoxin binding within the cortex. Cortical M(1) receptor binding was up to 30% lower than normal in the autistic subjects, and the difference reached significance in the parietal cortex. In both the parietal and frontal cortices, differences in nicotinic receptors assessed by [(3)H]epibatidine binding were significant and extensive (65%-73% lower in the autistic group than in the normal subjects); there were no differences in nicotine binding in the basal forebrain. Immunohistochemical analysis indicated lower levels of both the alpha(4) and beta(2) nicotinic receptor subunits in the parietal cortex. The M(1) receptor abnormality was not evident in the nonautistic group with mental retardation, although the lower [(3)H]epibatidine binding was apparent. In the basal forebrain, the level of brain-derived neurotrophic factor in the autistic group was three times as high as the level of the normal group. CONCLUSIONS: These neurochemical abnormalities implicate the cholinergic system in developmental disorders such as autism and suggest the potential for intervention based on cholinergic receptor modulation.

1.1.33. Farrington, C.P., Miller, E., Taylor, B. "MMR and autism: further evidence against a causal association." *Vaccine* 2001 Jun 14;19(27):3632-5.

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The hypothesis that MMR vaccines cause autism was first raised by reports of cases in which developmental regression occurred soon after MMR vaccination. A previous study found no evidence to support this hypothesis. It has recently been suggested that MMR vaccine might cause autism, but that the induction interval need not be short. The data from the earlier study were reanalysed to test this second hypothesis. Our results do not support this hypothesis, and provide further evidence against a causal association between MMR vaccination and autism.

1.1.34. Shevell, M.I., Majnemer, A., Rosenbaum, P., Abrahamowicz, M. Brain. "Etiologic determination of childhood developmental delay." *Dev* 2001 Jul;23(4):228-35.

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To determine the etiologic yield in young children with developmental delay referred to sub-specialty clinics for evaluation. Over an 18-month period, all children less than 5 years of age referred to the ambulatory pediatric neurology or developmental pediatrics clinics of the Montreal Children's Hospital for initial evaluation of a suspected developmental delay were enrolled. Features evident on history or physical examination were determined at intake as were the laboratory tests (and their rationale) requested by the evaluating physicians. Six months post initial assessment, detailed chart review was undertaken to determine if an etiology was found and the basis for such a determination. Bivariate and multivariate logistic regression was used to test for associations between factors present at intake and successful ascertainment of an underlying etiology. Two hundred and twenty-four children met study criteria. Etiologic yield varied across childhood developmental delay subtypes, and was 44/80 for global developmental delay [GDD] (55%), 13/22 for motor delay [MD] (59.1%), 3/72 for developmental language disorders [DLD] (4.2%), and 1/50 for autistic spectrum disorders [ASD] (2%). For GDD, the presence of historical features or findings on physical examination was associated with greater likelihood for successful etiologic determination with the following items significant in multiple logistic regression analysis; microcephaly, antenatal toxin exposure, focal findings. For MD, physical findings or the co-existence of a cerebral palsy symptom complex predicted a successful search for etiology. For both groups, the severity of the delay did not predict etiologic yield. For both groups, a small number of etiologic categories accounted for the majority of diagnoses made. Etiologic yield in childhood developmental delay is largely dependent on the specific developmental delay subtype. Paradigms for systematic evaluation of this common child health problem can be suggested, however they await validation.

1.1.35. Juul-Dam, N., Townsend, J., Courchesne, E. "Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population." *Pediatrics* 2001 Apr;107(4):E63.

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OBJECTIVES: To examine various pre-, peri-, and neonatal factors in autistic participants and in pervasive developmental disorder-not otherwise specified (PDD-NOS) participants and to compare the incidence of each factor to that of the normal population. **METHODS:** Seventy-four participants (66 males, 8 females) were diagnosed with autism at 2.5 through 4 years of age using the most accurate and up-to-date methods, including the Diagnostic and Statistical Manual of Mental Disorders and the Autism Diagnostic Interview-Revised. At age 5, all participants were reevaluated using the Diagnostic and Statistical Manual of Mental Disorders, the Autism Diagnostic Interview-Revised, the Childhood Autism Rating Scale, and the Autism Diagnostic Observation Schedule-Revised, resulting in 61 autistic and 13 PDD-NOS participants. Twenty-eight pre-, peri-, and neonatal factors were examined in these 2 groups using both medical records and parental interviews. Incidences were compared with those of the US population as reported in the Report of Final Natality Statistics, 1995. This grand scale population group was used to closely approximate comparison to a normal, unbiased population. Results were analyzed using the binomial probability test, with a P value of <.05, constituting a significant difference in incidence. A Bonferroni correction was applied to the data to adjust for the number of factors investigated. **RESULTS:** Although most of the factors showed comparable incidences between the index and control groups, several factors showed statistically significant differences. Following the Bonferroni correction, the autism group was found to have a significantly higher incidence of uterine bleeding, a lower incidence of maternal vaginal infection, and less maternal use of contraceptives during conception when compared with the general population. Similarly, the PDD-NOS group showed a higher incidence of hyperbilirubinemia when compared with the general population. **CONCLUSIONS:** The results of this study support previous findings suggesting a consistent association of unfavorable events in pregnancy, delivery, and the neonatal phase and the pervasive developmental disorders. However, interpretation of the meaningfulness of these results is difficult, as the specific complications that carried the highest risk of autism and PDD-NOS represented various forms of pathologic processes with no presently apparent unifying feature. Additional studies are needed to corroborate and strengthen these associations, as well as to determine the possibility of an underlying unifying pathological process. This study's analysis of obstetric and neonatal complications in combination with the use of participants diagnosed at an early age provides some interesting concepts to consider. Perhaps future research will confirm certain pre-, peri-, and neonatal associations that could be used to generate a high-risk historical profile with which to use in conjunction with currently employed diagnostic tools. This may, in turn, help to determine the reliability of a diagnosis of autism in younger children, leading to earlier intervention and assistance for an improved outcome in long-term functionality and quality of life.

1.1.36. Halsey, N.A., Hyman, S.L. "Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations." *Conference Writing Panel. Pediatrics* 2001 May;107(5):E84. Publication Types: Consensus Development Conference Review.

Conference convened in Oak Brook, Illinois, June 12-13, 2000.

BACKGROUND: Parents and physicians are understandably concerned about the causes and treatment of autism, a devastating disease that affects the entire family. Although much has been learned about autism, there are many gaps in our knowledge about what causes the disorder and how it can be prevented. Autistic symptoms occur along a spectrum, often referred to as autistic spectrum disorder (ASD). Concern has been raised about a possible association between measles-mumps-rubella (MMR) vaccine and inflammatory bowel disease (IBD) and ASD, especially autism with regression. Also, increased requests for educational services related to ASD have raised concerns about possible increases in the incidence of ASD. **METHODS:** On June 12-13, 2000, the American Academy of Pediatrics (AAP) convened a conference titled "New Challenges in Childhood Immunizations" in Oak Brook, Illinois. At this conference, parents, practitioners, and scientists presented information and research on MMR vaccine and ASD. Attendees included representatives from select AAP committees and sections as well as federal and other organizations that address related issues. The multidisciplinary panel of experts reviewed data on what is known about the pathogenesis, epidemiology, and genetics of ASD and the available data on hypothesized associations with IBD, measles, and MMR vaccine. Supplemental information was requested from authors who have proposed the hypotheses and other experts in relevant areas. **RESULTS:** Autism is a complex disorder of uncertain and probably multiple etiologies. Genetic predisposition to ASD may involve as many as 10 genes. Many experts believe that the abnormal brain development in autism occurs before 30 weeks' gestation in most instances. In utero rubella is a known cause of autism. Animal model data support the biologic plausibility that exposure to yet unrecognized infectious or other environmental agents could cause ASD. Several factors may contribute to apparent increases in incidence of ASD in recent years. Most data indicate increased recognition and reporting as primary factors, but the epidemiologic data are insufficient to determine if there has been a true increase in the incidence of ASD. Increased reporting of ASD in recent years has occurred long after the introduction of MMR vaccine in the United States in 1971 and widespread use of this vaccine in the 1970s for routine immunization of children at 12 to 15 months of age. Appropriate detailed studies are needed to define the true incidence and prevalence of ASD. Epidemiologic studies in Europe indicate no association between MMR vaccine and ASD. Some children with ASD have gastrointestinal symptoms, but an increased rate of any specific gastrointestinal disorder in children with ASD has not been established. Studies to detect evidence of measles virus in intestinal tissue specimens from patients with IBD or autism with gastrointestinal symptoms have not used uniform

techniques. Several laboratories have found no evidence of measles viruses in tissue specimens from patients with IBD, but 2 groups have found evidence of measles virus using different techniques. A group that found evidence of measles virus in affected tissue specimens from patients with IBD has also reported detecting portions of measles virus in peripheral blood lymphocytes and intestinal tissue specimens from patients with autism and gastrointestinal disorders. Finding a portion of a virus using molecular techniques does not constitute evidence for a causal relationship, because some viruses persist in unaffected hosts. Additional controlled studies in several laboratories are needed to determine if portions of measles virus persist in intestinal and other tissues of people with and without gastrointestinal disease and/or ASD. **CONCLUSIONS:** Although the possible association with MMR vaccine has received much public and political attention and there are many who have derived their own conclusions based on personal experiences, the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or IBD. Separate administration of measles, mumps, and rubella vaccines to children provides no benefit over administration of the combination MMR vaccine and would result in delayed or missed immunizations. Pediatricians need to work with families to ensure that children are protected early in the second year of life from these preventable diseases. Continued scientific efforts need to be directed to the identification of the causes of ASD.

1.1.37. Malek-Ahmadi, P. "Cytokines and etiopathogenesis of pervasive developmental disorders." *Med Hypotheses* 2001 Mar;56(3):321-4.

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Autistic disorder, also known as early infantile autism, is a developmental disorder of unknown etiology. However, there is some evidence to suggest that abnormalities of the immune system mediate the pathophysiology of autistic disorder. Cytokines, which play a pivotal role in initiating and maintaining immune responses, have been implicated in the etiopathogenesis of major neuropsychiatric disorders including autism. Cytokines are synthesized in the periphery, as well as in the central nervous system, and exert their effects by binding to their receptors in the nervous tissues. It is suggested that, in genetically predisposed individuals, overproduction or decreased synthesis of certain cytokines may result in neurodevelopmental arrest and/or neurotoxicity. Copyright 2001 Harcourt Publishers Ltd.

1.1.38. Binstock, T. "Intra-monocyte pathogens delineate autism subgroups." *Med Hypotheses* 2001 Apr;56(4):523-31.

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Immune panels of many autism-spectrum children reveal signs of atypical infections and shifted cell counts. In conjunction with trait-related cerebral hypometabolism and hypoperfusion, these findings suggest a hypothesis: Several

autism-spectrum subgroups derive from intra-monocyte pathogens such as measles virus, cytomegalovirus, human herpesvirus 6, and *Yersinia enterocolitica*. Furthermore, with much inter-child variation, their effects manifest as diminished hematopoiesis, impaired peripheral immunity, and altered blood-brain barrier function often accompanied by demyelination. In some such children, one or more of these pathogens persists as a chronic-active, seemingly subclinical infection etiologically significant to the child's autistic traits. Within these subgroups, immune impairments and atypical infections may be treatable. Copyright 2001 Harcourt Publishers Ltd.

1.1.39. Happe, F., Briskman, J., Frith, U.J. "Exploring the cognitive phenotype of autism: weak "central coherence" in parents and siblings of children with autism: I. Experimental tests." *Child Psychol Psychiatry* 2001 Mar;42(3):299-307.

Institute of Psychiatry, Kings College, London.

Previous twin and family studies have indicated that there are strong genetic influences in the etiology of autism, and provide support for the notion of a broader phenotype in first-degree relatives. The present study explored this phenotype in terms of one current cognitive theory of autism. Parents and brothers of boys with autism, boys with dyslexia, and normal boys were given tests of "central coherence", on which children with autism perform unusually well due to an information-processing bias favouring part/detail processing over processing of wholes/meaning. Results indicated that fathers of boys with autism, as a group, showed piecemeal processing across four tests of central coherence. This was not true for any other group. These findings raise the possibility that the broader autism phenotype may include a "cognitive style" (weak central coherence) that can confer information-processing advantages.

1.1.40. Feng, J., Zheng, J., Gelernter, J., Kranzler, H., Cook, E., Goldman, D., Jones, I.R., Craddock, N., Heston, L.L., Delisi, L., Peltonen, L., Bennett, W.P., Sommer, S.S. "An in-frame deletion in the alpha(2C) adrenergic receptor is common in African-Americans." *Mol Psychiatry* 2001 Mar;6(2):168-72.

Department of Molecular Genetics, City of Hope National Medical Center & Beckman Research Institute, 1500 East Duarte Road, Duarte, CA 91010, USA.

Alpha(2) adrenergic receptors are activated by adrenaline and noradrenaline, and three subtypes (ie, A, B, C) have differential affinities for antagonists and medications. The alpha(2c) adrenergic receptor (ADRA2C), located on chromosome 4p16.3, is a candidate gene for schizophrenia because it binds clozapine, an atypical neuroleptic useful for treatment-resistant schizophrenia. In addition, ADRA2C binds clonidine which is prescribed for three psychiatric diseases. This report communicates the findings of the genetic scanning of this gene of very tough GC content. The complete coding sequences and splice junctions were scanned with [DOVAM]-S in 104 schizophrenics, and pilot probes of patients with alcoholism (41 patients), cocaine abuse (25

patients), puerperal psychosis (30 patients), attention deficient/hyperactivity disorder (25 patients) and autism (25 patients). Six sequence variants were found, including five silent polymorphisms (allele frequencies 0.6–25%) and an in-frame deletion of a homologous repeat at nucleotides 967–978 (ie, TIDRU(1)). Genotyping of the normal two repeat unit of the Third Intracytoplasmic Domain Repeat Unit (TIDRU(2)) and the deleted variant (TIDRU(1)) revealed that TIDRU(1) had allelic frequencies of 39% (11/28) and 3.5% (6/172) in African-American and Caucasian schizophrenics, respectively, and it occurred with equal frequency in controls (44%, 31/70 and 3.0%, 6/198). TIDRU(1) occurs at a location similar to the third intracytoplasmic 48-nucleotide repeat unit in the DRD4 that is associated with ADHD. Although these data do not suggest an association of TIDRU(1) with schizophrenia, additional studies are needed to see whether TIDRU(1) confers a clinical phenotype.

1.1.41. Rastam, M., Bjure, J., Vestergrén, E., Uvebrant, P., Gillberg, I.C., Wentz, E., Gillberg, C. "Regional cerebral blood flow in weight-restored anorexia nervosa: a preliminary study". *Dev Med Child Neurol* 2001 Apr;43(4):239-42.

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Twenty-one individuals (19 females, two males) with teenage-onset anorexia nervosa (AN), 19 of whom were weight restored, were assessed using single-photon emission computed tomography (SPECT) 7 years after onset of AN, at a mean age of 22 years. For comparison we recruited a younger group without neuropsychiatric disorder (mean age 9:8 years; five females, four males) who underwent SPECT at follow-up after an operation for coarctation of the aorta or because of lymphatic leukaemia. Ethical considerations precluded the study of regional cerebral blood flow (rCBF) in participants with completely normal development. The group with AN showed marked hypoperfusion of temporal, parietal, occipital, and orbitofrontal lobes compared to the contrast group. RCBF was not correlated to body mass index in any of the groups. Results suggest that, even long after re-feeding has occurred, AN may be associated with moderate to severe cerebral blood flow hypoperfusion in the temporoparietal (or temporoparietooccipital) region and in the orbitofrontal region. A limitation of the study is that the young contrast group in this study could be expected to have a higher global rCBF than the group with AN. However, this should not significantly affect the relative values used in this study.

1.1.42. Stoll, C. "Problems in the diagnosis of fragile X syndrome in young children are still present." *Am J Med Genet* 2001 Apr 22;100(2):110-5.

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Fragile X syndrome is common; its prevalence approaches 1 per 5,000. Fragile X syndrome is the most common inherited cause of mental retardation. Many professionals must deal with fragile X individuals on a daily basis. However, despite

the diverse information on the epidemiology, clinical features, unique pattern of inheritance, cytogenetic, and molecular diagnosis and scales for the diagnosis of this syndrome, the diagnosis of fragile X syndrome is still not always made by the patients' specialists. Here we present the difficulties in the diagnosis of fragile X syndrome in 11 children under 8 years of age, 10 boys and one girl. We report data on initial symptoms, behavioral features, and physical and mental development before molecular studies were considered. The possible causes for the diagnosis delay were multiple: nonspecific features (e.g., macrocephaly, overgrowth, obesity), unremarkable physical examination, family history apparently noncontributory, and lack of or delayed molecular testing. Careful clinical examination of young children and DNA screening in case of doubt, and education of professionals in medical specialty areas, behavioral sciences, education, and other fields are recommended. Copyright 2001 Wiley-Liss, Inc.

1.1.43. Williams, G., King, J., Cunningham, M., Stephan, M., Kerr, B., Hersh, J.H. "Fetal valproate syndrome and autism: additional evidence of an association." *Dev Med Child Neurol* 2001 Mar;43(3):202-6.

University of Louisville Child Evaluation Center, KY 20402-3828, USA.

Autism has been described in association with a variety of medical and genetic conditions. We previously reported on a patient whose clinical phenotype was compatible with both fetal valproate syndrome (FVS) and autism. Here we present five additional patients with FVS and autism. In all five of our patients, there was evidence of cognitive deficits, manifestations of autism, and typical phenotypic characteristics of FVS. The association between this known teratogen and autism has both clinical and research implications.

1.1.44. Manning, J.T., Baron-Cohen, S., Wheelwright, S., Sanders, G. "The 2nd to 4th digit ratio and autism." *Dev Med Child Neurol* 2001 Mar;43(3):160-4.

Population and Evolutionary Biology Research Group, School of Biological Sciences, University of Liverpool, United Kingdom.

It has been suggested that autism may arise as the result of exposure to high concentrations of prenatal testosterone. There is evidence that the ratio of the lengths of the 2nd and 4th digit (2D:4D) may be negatively correlated with prenatal testosterone. We measured 2D:4D in 95 families recruited via the National Autistic Society, UK. The sample comprised a total 72 children with autism (62 males, 10 females; age range 2 to 14 years), including 23 children (20 males, three females) with Asperger syndrome (AS), 34 siblings, 88 fathers, 88 mothers and sex- and age-matched control participants. We found that the 2D:4D ratios of children with autism, their siblings, fathers and mothers were lower than population normative values. Children with AS, who share the social and communicative symptoms of autism but have normal or even high IQ, had higher 2D:4D ratios than children with autism

but lower ratios than population normative values. There were positive associations between 2D:4D ratios of children with autism and the ratios of their relatives. Children with autism had lower than expected 2D:4D ratios and children with AS higher ratios than expected in relation to their fathers' 2D:4D ratio. It was concluded that 2D:4D ratio may be a possible marker for autism which could implicate prenatal testosterone in its aetiology.

1.1.45. DeWilde, S., Carey, I.M., Richards, N., Hilton, S.R., Cook, D.G. "Do children who become autistic consult more often after MMR vaccination?" *Br J Gen Pract* 2001 Mar;51(464):226-7.

Department of General Practice and Primary Care, George's Hospital Medical School, London SW17 0RE.

A close temporal association has been reported between the measles, mumps, and rubella (MMR) vaccination and dramatic behavioural decline in children subsequently diagnosed as autistic. We hypothesised that such a decline would be reflected in increased consultations with the child's general practitioner. The Doctor's Independent Network database was used to examine whether children subsequently diagnosed as autistic consulted more frequently than controls after MMR vaccination. No difference in consulting behaviour was seen in the six months post MMR. Any dramatic effect of MMR on behaviour seems unlikely.

1.1.46. Smeeth, L., Hall, A.J., Lombonne, E., Rodrigues, L.C., Huang, X., Smith, P.G. "A case-control study of autism and mumps-measles-rubella vaccination using the general practice research database: design and methodology." *BMC Public Health* 2001;1(1):2.

Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK.

BACKGROUND: An association between mumps-measles-rubella (MMR) vaccination and the onset of symptoms typical of autism has recently been suggested. This has led to considerable concern about the safety of the vaccine. **METHODS:** A matched case-control study using data derived from the United Kingdom General Practice Research Database. Children with a possible diagnosis of autism will be identified from their electronic health records. All diagnoses will be validated by a detailed review of hospital letters and by using information derived from a parental questionnaire. Ten controls per case will be selected from the database. Conditional logistic regression will be used to assess the association between MMR vaccination and autism. In addition case series analyses will be undertaken to estimate the relative incidence of onset of autism in defined time intervals after vaccination. The study is funded by the United Kingdom Medical Research Council. **DISCUSSION:** Electronic health databases offer tremendous opportunities for evaluating the adverse effects of vaccines. However there is much scope for bias and confounding. The rigorous validation of all diagnoses and the collection of additional information by parental questionnaire in this study are essential to minimise the possibility of misleading results.

1.1.47. Kaye, J.A., del Mar Melero-Montes, M., Jick, H. "Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis." *BMJ* 2001 Feb 24;322(7284):460-3.

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OBJECTIVE: To estimate changes in the risk of autism and assess the relation of autism to the mumps, measles, and rubella (MMR) vaccine. **DESIGN:** Time trend analysis of data from the UK general practice research database (GPRD). **SETTING:** General practices in the United Kingdom. **SUBJECTS:** Children aged 12 years or younger diagnosed with autism 1988-99, with further analysis of boys aged 2 to 5 years born 1988-93. **Main outcome measures:** Annual and age specific incidence for first recorded diagnoses of autism (that is, when the diagnosis of autism was first recorded) in the children aged 12 years or younger; annual, birth cohort specific risk of autism diagnosed in the 2 to 5 year old boys; coverage (prevalence) of MMR vaccination in the same birth cohorts. **RESULTS:** The incidence of newly diagnosed autism increased sevenfold, from 0.3 per 10 000 person years in 1988 to 2.1 per 10 000 person years in 1999. The peak incidence was among 3 and 4 year olds, and 83% (254/305) of cases were boys. In an annual birth cohort analysis of 114 boys born in 1988-93, the risk of autism in 2 to 5 year old boys increased nearly fourfold over time, from 8 (95% confidence interval 4 to 14) per 10 000 for boys born in 1988 to 29 (20 to 43) per 10 000 for boys born in 1993. For the same annual birth cohorts the prevalence of MMR vaccination was over 95%. **CONCLUSIONS:** Because the incidence of autism among 2 to 5 year olds increased markedly among boys born in each year separately from 1988 to 1993 while MMR vaccine coverage was over 95% for successive annual birth cohorts, the data provide evidence that no correlation exists between the prevalence of MMR vaccination and the rapid increase in the risk of autism over time. The explanation for the marked increase in risk of the diagnosis of autism in the past decade remains uncertain.

1.1.48. Einat, H., Belmaker, R.H. "The effects of inositol treatment in animal models of psychiatric disorders." *J Affect Disord* 2001 Jan;62(1-2):113-21. Publication Types: Review, Review, Tutorial.

Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel.

Clinical trials indicate that inositol may be effective in the treatment of patients with depression, panic disorder and obsessive compulsive disorder (OCD), but not in the treatment of patients with schizophrenia, Alzheimer's disease, ADHD or autism. This spectrum of clinical action parallels that of serotonin selective reuptake inhibitors (SSRIs), but inositol is a precursor in the phosphatidylinositol cycle, a second messenger system distal to the receptor for 5HT-2. To study its mechanism of therapeutic action there is a need to test inositol's activity in animal models of psychopathology. In rats, chronic inositol was demonstrated to increase activity levels, reduce immobility time in the forced swim test and in

the reserpine-induced hypoactivity models of depression, and reduce anxiety-like behaviors in the elevated plus-maze. The reduction in anxiety-like behaviors appears to be related to baseline levels of activity. Inositol treatment was not observed to have any effect on amphetamine-induced hyperactivity, apomorphine-induced stereotypy, or on the performance of memory tasks by monkeys. Clinical controlled trials of inositol in patients with depression, panic disorder, and OCD were small, and positive psychoactive effects in animals clearly strengthen the case for further clinical trials and potential for general therapeutic use in humans.

1.1.49. Goldberg, M.C., Landa, R., Lasker, A., Cooper, L., Zee, D.S. "Evidence of normal cerebellar control of the vestibulo-ocular reflex (VOR) in children with high-functioning autism." *J Autism Dev Disord* 2000 Dec;30(6):519-24.

The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA.

The effect of "tilt-suppression" on post-rotatory vestibular nystagmus was investigated to assess the function of the caudal cerebellar vermis (lobules IX and X, or nodulus and uvula) in 13 school-age children with high-functioning autism (HFA) and 10 normal controls. Tilt-suppression of the vestibulo-ocular reflex (VOR) refers to the decreasing of the duration of post-rotatory vestibular nystagmus that occurs when the head is moved out of the plane in which it was located during the previous sustained constant-velocity rotation. The participant is rotated in a vestibular chair with the head upright and then the head is tilted forward just after the chair stops rotating. Such tilt-suppression is impaired with lesions of the cerebellar nodulus and portions of the uvula. Results show that children with HFA have normal post-rotatory nystagmus with the head upright and normal attenuation of post-rotatory nystagmus induced by head tilt. These behavioral findings suggest that lobules IX and X of the cerebellum are spared in high-functioning autism.

1.1.50. Sabbagh, M.A. "Neural correlates of theory-of-mind reasoning: an event-related potential study." *Taylor M.Psychol Sci* 2000 Jan;11(1):46-50.

University of Oregon, USA. sabbagh@umich.edu.

Everyday understanding of human behavior rests on having a theory of mind—the ability to relate people's actions to underlying mental states such as beliefs and desires. It has been suggested that an impaired theory of mind may lie at the heart of psychological disorders that are characterized by deficits in social understanding, such as autism. In this study, we employed the event-related potential methodology to index the activity of neural systems that are engaged during theory-of-mind reasoning in adults. Specifically, neural activity elicited by tasks that required thinking about mental as compared with nonmental representations (i.e., beliefs vs. photographs) was characterized by a focally enhanced positivity over left frontal areas, which was diminished over left parietal areas. These findings provide an important perspective on both children's theory-of-mind development and the neurobiology of disorders in which theory of mind seems to be impaired.

1.1.51. Pareek, M., Pattison, H.M. "The two-dose measles, mumps, and rubella (MMR) immunisation schedule: factors affecting maternal intention to vaccinate." *Br J Gen Pract* 2000 Dec;50(461):969-71.

Department of Primary Care and General Practice, University of Birmingham Medical School.

BACKGROUND: In the light of sub-optimal uptake of the measles, mumps, and rubella (MMR) vaccination, we investigated the factors that influence the intentions of mothers to vaccinate. **METHOD:** A cross-sectional survey of 300 mothers in Birmingham with children approaching a routine MMR vaccination was conducted using a postal questionnaire to measure: intention to vaccinate, psychological variables, knowledge of the vaccine, and socioeconomic status. The vaccination status of the children was obtained from South Birmingham Child Health Surveillance Unit. **RESULTS:** The response rate was 59%. Fewer mothers approaching the second MMR vaccination (Group 2) intended to take their children for this vaccination than Group 1 (mothers approaching the first MMR vaccination) (Mann-Whitney U = 2180, $P < 0.0001$). Group 2 expressed more negative beliefs about the outcome of having the MMR vaccine ('vaccine outcome beliefs') (Mann-Whitney U = 2155, $P < 0.0001$), were more likely to believe it was 'unsafe' ($\chi^2 = 9.114$, $P = 0.004$) and that it rarely protected ($\chi^2 = 6.882$, $P = 0.014$) than Group 1. The commonest side-effect cited was general malaise, but 29.8% cited autism. The most trusted source of information was the general practitioner but the most common source of information on side-effects was television (34.6%). Multiple linear regression revealed that, in Group 1, only 'vaccine outcome beliefs' significantly predicted intention (77.1% of the variance). In Group 2 'vaccine outcome beliefs', attitude to the MMR vaccine, and prior MMR status all predicted intention (93% of the variance). **CONCLUSION:** A major reason for the low uptake of the MMR vaccination is that it is not perceived to be important for children's health, particularly the second dose. Health education from GPs is likely to have a considerable impact.

1.1.52. Court, J.A., Martin-Ruiz, C., Graham, A., Perry, E.J. "Nicotinic receptors in human brain: topography and pathology." *Chem Neuroanat* 2000 Dec;20(3-4):281-98. Publication Types: Review, Review Literature.

Joint MRC-Newcastle University, Development in Clinical Brain Ageing, MRC Building, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, UK. j.a.court@ncl.ac.uk.

Brain nicotinic acetylcholine receptors (nAChR) are a class of ligand-gated channels composed of alpha and beta subunits with specific structural, functional and pharmacological properties. They participate in the physiological and behavioural effects of acetylcholine and mediate responses to nicotine. They are associated with numerous transmitter systems and their expression is altered during development and ageing as well as in diseases such as autism, schizophrenia, Alzheimer's disease, Parkinson's disease and Lewy body dementia. Nicotinic receptors containing a number of different subunits are highly expressed during early human

development. Disorders believed to be associated with abnormal brain maturation involve deficits in both alpha4beta2, in the case of autism, and alpha7 possibly in addition to alpha4beta2 nAChRs in the case of schizophrenia. In ageing and age-related neurodegenerative disorders nAChR deficits are predominantly associated with alpha4-containing receptors, although some studies also indicate the involvement of alpha3 and alpha7 subunits. Whilst ageing appears to be associated with reductions in subunit mRNA as well as protein expression, in Alzheimer's disease only protein loss is apparent. Nicotinic therapy may be of benefit in a number of neurological conditions, however studies evaluating further both the distribution of specific subunit involvement and the correlation of nAChR deficits with clinical symptoms are required to inform therapeutic strategy.

1.1.53. Fidler, D.J., Bailey, J.N., Smalley, S.L. "Macrocephaly in autism and other pervasive developmental disorders." *Dev Med Child Neurol* 2000 Nov;42(11):737-40.

UCLA Neuropsychiatric Institute, Los Angeles, CA, USA.

To assess the prevalence of macrocephaly (head circumference $>$ or = 1.88 standard deviations above normative data for age and sex or $>$ 97th centile) in autism and other pervasive developmental disorders, 41 children with autism, and a comparison group of 21 children with tuberous sclerosis complex (TSC) or an unspecified seizure disorder were studied. Familiarity of head circumference was also assessed from measurements of 133 first-degree relatives. Significantly higher rates of macrocephaly were found in probands with autism (12.2%) and their first-degree relatives (15.5%) when compared against a published normative sample. The incidence of macrocephaly in the comparison group of probands with TSC and seizure disorder (9.5%) and their first-degree relatives (8.3%) was higher than normative data as well, although the relation between macrocephaly and autism was more pronounced. Head circumference and extreme scores reflecting macrocephaly were moderately heritable in the present sample ($H^2 = 0.47$). The increased prevalence of macrocephaly in relatives of children with autism compared with control children suggests that this characteristic may be a familial risk factor in the pathogenesis of autism.

1.1.54. Kotsopoulos, S. "Uncertainties in aetiology and treatment of infantile autism—assumptions and evidence." *Med Health Care Philos* 2000;3(2):175-8. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Faculty of Medicine, University of Calgary, Canada.

Uncertainty in the field of child psychiatry may at times lead to groundless assumptions about the aetiology and pathology of psychiatric disorders of childhood. Treatment based on non-validated assumptions may be ineffective and may cause more harm than good. The case is presented of infantile autism which was at first attributed by clinicians to a specific negative effect of parents on their children. Evidence grounded on research did subsequently refute the assumption implicating the parents in the aetiology of this disorder. An explanatory assumption can become evidence if it is tested and found valid.

To avoid serious errors in the understanding and treatment of child psychiatric disorders, the clinician should always consider critically assumptions and opinion, provided in lieu of evidence.

1.1.55. Yeates-Frederikx, M.H., Nijman, H., Logher, E., Merckelbach, H.L. "Birth patterns in mentally retarded autistic patients." *J Autism Dev Disord* 2000 Jun;30(3):257-62.

Psychiatric Hospital Welterhof, Heerlen, The Netherlands. volkoren@wxs.nl.

Some studies claim to have shown that, compared to the general population, autistic children are born more often in the spring. The current study sought to replicate this finding in a large Dutch sample of mentally retarded autistic patients. Birth data for 1,031 patients with a diagnosis of "Infantile Autism" or "other psychoses with origin specific to childhood" were compared to those of the Dutch national population. Separate analyses were performed on diagnostic subgroups (i.e., infantile autism vs. other psychoses with origin specific to childhood), gender, and intelligence. No evidence was found to suggest that autism is characterized by a deviant birth pattern.

1.1.56. Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., Van Amelsvoort, T., Robertson, D.M., Rowe, A., Phillips, M., McAlonan, G., Howlin, P., Murphy, D.G. "The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions." *Brain* 2000 Nov;123 (Pt 11):2203-12.

Departments of Psychological Medicine and Neuroimaging, Institute of Psychiatry, Kings College, Department of Psychology, St George's Hospital Medical School, London, United Kingdom.

Although high-functioning individuals with autistic disorder (i.e. autism and Asperger syndrome) are of normal intelligence, they have life-long abnormalities in social communication and emotional behaviour. However, the biological basis of social difficulties in autism is poorly understood. Facial expressions help shape behaviour, and we investigated if high-functioning people with autistic disorder show neurobiological differences from controls when processing emotional facial expressions. We used functional MRI to investigate brain activity in nine adults with autistic disorder (mean age +/- standard deviation 37 +/- 7 years; IQ 102 +/- 15) and nine controls (27 +/- 7 years; IQ 116 +/- 10) when explicitly (consciously) and implicitly (unconsciously) processing emotional facial expressions. Subjects with autistic disorder differed significantly from controls in the activity of cerebellar, mesolimbic and temporal lobe cortical regions of the brain when processing facial expressions. Notably, they did not activate a cortical 'face area' when explicitly appraising expressions, or the left amygdala region and left cerebellum when implicitly processing emotional facial expressions. High-functioning people with autistic disorder have biological differences from controls when consciously and unconsciously processing facial emotions, and these differences are most likely to be neurodevelopmental in origin.

This may account for some of the abnormalities in social behaviour associated with autism.

1.1.57. Afzal, M.A., Pipkin, P.A., Minor, P.D. "Absence of chicken myelin basic protein residues in commercial formulations of MMR vaccine." *Vaccine* 2000 Oct 15;19(4-5):442-6.

Division of Virology, National Institute for Biological Standards and Control, South Mimms, Blanche Lane, Potters Bar, EN6 3QG, Hertfordshire, UK. mafzal@nibsc.ac.uk.

Several preparations of MMR vaccines and their progenitor monovalent vaccine bulks produced by two different manufacturers were examined serologically for the presence of chicken myelin basic protein (MBP) residues. The products were challenged against several commercial preparations of anti-hMBP antisera that reacted positively with the control MBP preparations of human and chicken origins. There was no evidence of the presence of MBP components in MMR vaccines or their progenitor vaccine bulks as shown by the reactivity profiles of the antibody preparations against control and test antigens.

1.1.58. DuVernoy, T.S., Braun, M.M. "Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998." *Pediatrics* 2000 Oct;106(4):E52.

Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20852-1428, USA.

BACKGROUND: A hypotonic-hyporesponsive episode (HHE) is the sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis that occurs within 48 hours after childhood immunizations. This syndrome has been primarily associated with pertussis-containing vaccines administered to children <2 years of age, and has been estimated to occur once every 1750 diphtheria-tetanus-pertussis (DTwP) vaccinations. Previous studies of HHE were limited by small numbers of cases and, sometimes, by limited details of the event. **OBJECTIVES:** To characterize a large number of HHE cases reported to the Vaccine Adverse Event Reporting System (VAERS), to assist clinicians in identifying HHE, and to assist researchers in investigating the risk factors, cause, and pathogenesis of this syndrome. **METHODS:** More than 40,000 VAERS reports received between 1996 and 1998 were screened for HHE by a computer algorithm and reviewed, and a telephone follow-up questionnaire was administered to the witness of HHE. **RESULTS:** There were 215 HHE cases, all nonfatal. The median age of onset of HHE was 4.0 months (range: 1.1-107 months). Over half of the reports (53%) concerned females. The median birth weight was 3.36 kg (range: 1.27-4.96 kg); 4.7% had a birth weight <2500 g. The median interval between vaccination and HHE was 210 minutes (range: 1 minute-2 days). Among children with HHE who were <24 months of age, the episode occurred within 5 minutes in only 8.5%, compared with 66.7% of children with HHE >24 months of age. There were no relevant findings regarding family medical history or the mothers' gestational

history. Nearly all of the children (98.6%) returned to their prevaccination state according to the telephone questionnaire; median time to return was 6 hours (range: 1 minute- 4 months). The 3 children reported as not returning to their prevaccination state all had VAERS reports submitted after they developed conditions (autism, complex partial epilepsy, and developmental delays with infantile spasms) that are not known to be causally associated with immunization. The vast majority of children (93%) with HHE received a pertussis-containing vaccine, either diphtheria-tetanus-acellular pertussis (DTaP, 28%), DTwP (11%), or diphtheria-tetanus-pertussis-Haemophilus influenzae type b (DTwP-HIB, 61%). During the HHE episode, 90.1% of the children had pallor and 49% had cyanosis. Because of the HHE event, 6.8% of children had had all vaccines withheld as of the date of the interview. Of the remainder, 66.5% of children have had 1 or more subsequent vaccinations or vaccine components withheld, and 26.7% have not had any subsequent vaccinations withheld. Only 1 child was reported to have had a repeat episode of HHE, occurring after hepatitis B vaccination. From 1996 to 1998, the number of HHE reports decreased from 99 to 38, when the predominant pertussis vaccine administered to infants changed from whole-cell to acellular. **CONCLUSION:** This study represents the largest published case series of children with HHE and supports the generally benign, self-limited, nonrecurrent nature of this syndrome. Although HHE has been less frequently reported to VAERS after increased use of DTaP, HHE does occur after the administration of DTaP and other nonpertussis-containing vaccines. Although most parents and pediatricians withheld the pertussis component of subsequent vaccinations, many did not, with no reported adverse events occurring in the children after the subsequent immunizations. Restricting the definition of HHE to a more narrow age range (eg, <2 years of age) is also proposed because most of the older children probably experienced vasovagal syncope rather than HHE within 5 minutes of immunization.

1.1.59. Howard, M.A., Cowell, P.E., Boucher, J., Broks, P., Mayes, A., Farrant, A., Roberts, N. **"Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism."** *Neuroreport* 2000 Sep 11;11(13):2931-5.

Magnetic Resonance and Image Analysis Research Centre, University of Liverpool, UK.

In this study we report a convergence of behavioural and neuroanatomical evidence in support of an amygdala hypothesis of autism. We find that people with high-functioning autism (HFA) show neuropsychological profiles characteristic of the effects of amygdala damage, in particular selective impairment in the recognition of facial expressions of fear, perception of eye-gaze direction, and recognition memory for faces. Using quantitative magnetic resonance (MR) image analysis techniques, we find that the same individuals also show abnormalities of medial temporal lobe (MTL) brain structure, notably bilaterally enlarged amygdala volumes. These results combine to suggest that developmental malformation of the amygdala may underlie the social-cognitive impairments characteristic of HFA. This

malformation may reflect incomplete neuronal pruning in early development.

1.1.60. Spencer, J., O'Brien, J., Riggs, K., Braddick, O., Atkinson, J., Wattam-Bell, J. **"Motion processing in autism: evidence for a dorsal stream deficiency."** *Neuroreport* 2000 Aug 21;11(12):2765-7.

Department of Psychology, London Guildhall University, UK.

We report that motion coherence thresholds in children with autism are significantly higher than in matched controls. No corresponding difference in form coherence thresholds was found. We interpret this as a specific deficit in dorsal stream function in autism. To examine the possibility of a neural basis for the perceptual and motor related abnormalities frequently cited in autism we tested 23 children diagnosed with autistic disorder, on two tasks specific to dorsal and ventral cortical stream functions. The results provide evidence that autistic individuals have a specific impairment in dorsal stream functioning. We conclude that autism may have common features with other developmental disorders and with early stages of normal development, perhaps reflecting a greater vulnerability of the dorsal system.

1.1.61. Ohnishi, I., Matsuda, H., Hashimoto, T., Kunihiro, T., Nishikawa, M., Uema, T., Sasaki, M. **"Abnormal regional cerebral blood flow in childhood autism."** *Brain* 2000 Sep;123 (Pt 9):1838-44.

Department of Radiology, National Center Hospital of Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira City, Tokyo, Japan. tohnishi@hotmail.com.

Neuroimaging studies of autism have shown abnormalities in the limbic system and cerebellar circuits and additional sites. These findings are not, however, specific or consistent enough to build up a coherent theory of the origin and nature of the brain abnormality in autistic patients. Twenty-three children with infantile autism and 26 non-autistic controls matched for IQ and age were examined using brain-perfusion single photon emission computed tomography with technetium-99m ethyl cysteinate dimer. In autistic subjects, we assessed the relationship between regional cerebral blood flow (rCBF) and symptom profiles. Images were anatomically normalized, and voxel-by-voxel analyses were performed. Decreases in rCBF in autistic patients compared with the control group were identified in the bilateral insula, superior temporal gyri and left prefrontal cortices. Analysis of the correlations between syndrome scores and rCBF revealed that each syndrome was associated with a specific pattern of perfusion in the limbic system and the medial prefrontal cortex. The results confirmed the associations of (i) impairments in communication and social interaction that are thought to be related to deficits in the theory of mind (ToM) with altered perfusion in the medial prefrontal cortex and anterior cingulate gyrus, and (ii) the obsessive desire for sameness with altered perfusion in the right medial temporal lobe. The perfusion abnormalities seem to be related to the cognitive dysfunction observed in autism, such as deficits in ToM, abnormal responses to sensory stimuli, and the

obsessive desire for sameness. The perfusion patterns suggest possible locations of abnormalities of brain function underlying abnormal behaviour patterns in autistic individuals.

1.1.62. Rice, D., Barone, S. Jr. "Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models." *Environ Health Perspect* 2000 Jun;108 Suppl 3:511-33. Publication Types: Review, Review, Tutorial.

National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA.

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans.

1.1.63. Satoj, M., Matsuishi, T., Yamada, S., Yamashita, Y., Ohtaki, E., Mori, K., Riikonen, R., Kato, H., Percy, A.K. "Decreased cerebrospinal fluid levels of beta-phenylethylamine in patients with Rett syndrome." *Ann Neurol* 2000 Jun;47(6):801-3.

Department of Pediatrics and Child Health, Kurume University School of Medicine, Japan.

To clarify the mechanism of brain impairment in Rett syndrome, we measured the cerebrospinal fluid levels of beta-phenylethylamine (PEA) in 17 patients with Rett syndrome. Findings were compared with those obtained in age-matched controls and diseased controls. The cerebrospinal fluid level of PEA was significantly lower in patients with Rett syndrome

than in the controls (31% of control values). The alteration in the cerebrospinal fluid level of PEA may reflect dopamine system impairment in Rett syndrome.

1.1.64. Shevell, M.I., Majnemer, A., Rosenbaum, P., Abrahamowicz, M. "Etiologic yield of subspecialists' evaluation of young children with global developmental delay." *J Pediatr* 2000 May;136(5):593-8.

Departments of Neurology/Neurosurgery, Pediatrics, and Epidemiology and Biostatistics and School of Physical & Occupational Therapy, McGill University, Montreal, Quebec, Canada.

OBJECTIVE: To determine the etiologic yield of subspecialists' evaluation of young children with global developmental delay. In addition, variables that may predict finding an underlying etiology were also identified. **METHODS:** All children <5 years of age, referred over an 18-month period to subspecialty services for initial evaluation of a suspected developmental delay, were prospectively enrolled. Diagnostic yield was ascertained after the completion of clinical assessments and laboratory investigations requested by the evaluating physician. **RESULTS:** Ninety-nine children (71 boys) were found to have global developmental delay; 96% had a mild or moderate delay documented. An etiologic diagnosis was determined in 44. Four diagnoses (cerebral dysgenesis, hypoxic-ischemic encephalopathy, toxin exposure, chromosomal abnormalities) accounted for 34 of 44 (77%) of the diagnoses made. The presence of co-existing autistic traits was associated with significantly decreased diagnostic yield (0/19 vs 44/80, $P < .0001$), whereas specific historical features (eg, family history, toxin exposure, and perinatal difficulty; 23/32 vs 21/67, $P = .0002$) and findings on physical examination (eg, dysmorphology, microcephaly, and focal motor findings; 35/48 vs 9/51, $P < .0001$) were significantly associated with identifying a diagnosis. Multiple logistic regression analysis identified antenatal toxin exposure, microcephaly, focal motor findings, and the absence of autistic traits as significant predictor variables for the identification of an etiology. **CONCLUSION:** An etiologic diagnosis is often possible in the young child with global developmental delay, particularly in the absence of autistic features. Etiologic yield is augmented by presence of specific findings on history or physical examination on initial assessment.

1.1.65. Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C. "The amygdala theory of autism." *Neurosci Biobehav Rev* 2000 May;24(3):355-64. Publication Types: Review, Review, Tutorial.

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Brothers (Brothers L. Concepts in Neuroscience 1990;1:27-51) proposed a network of neural regions that comprise the "social brain", which includes the amygdala. Since the childhood psychiatric condition of autism involves deficits in "social intelligence", it is plausible that autism may be caused by an amygdala abnormality. In this paper we review the evidence

for a social function of the amygdala. This includes reference to the Kluver-Bucy syndrome (which Hetzler and Griffin suggested may serve as an animal model of autism). We then review evidence for an amygdala deficit in people with autism, who are well known to have deficits in social behaviour. This includes a detailed summary of our recent functional magnetic resonance imaging (fMRI) study involving judging from the expressions of another person's eyes what that other person might be thinking or feeling. In this study, patients with autism or AS did not activate the amygdala when making mentalistic inferences from the eyes, whilst people without autism did show amygdala activity. The amygdala is therefore proposed to be one of several neural regions that are abnormal in autism. We conclude that the amygdala theory of autism contains promise and suggest some new lines of research.

1.1.66. Kawashima, H., Mori, T., Kashiwagi, Y., Takekuma, K., Hoshika, A., Wakefield, A. "Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism." *Dig Dis Sci* 2000 Apr;45(4):723-9.

Department of Paediatrics, Tokyo Medical University, Japan.

It has been reported that measles virus may be present in the intestine of patients with Crohn's disease. Additionally, a new syndrome has been reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases soon after MMR vaccine. It is not known whether the virus, if confirmed to be present in these patients, derives from either wild strains or vaccine strains. In order to characterize the strains that may be present, we have carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in eight patients with Crohn's disease, three patients with ulcerative colitis, and nine children with autistic enterocolitis. As controls, we examined healthy children and patients with SSPE, SLE, HIV-1 (a total of eight cases). RNA was purified from PBMC by Ficoll-paque, followed by reverse transcription using AMV; cDNAs were subjected to nested PCR for detection of specific regions of the hemagglutinin (H) and fusion (F) gene regions. Positive samples were sequenced directly, in nucleotides 8393-8676 (H region) or 5325-5465 (from noncoding F to coding F region). One of eight patients with Crohn disease, one of three patients with ulcerative colitis, and three of nine children with autism, were positive. Controls were all negative. The sequences obtained from the patients with Crohn's disease shared the characteristics with wild-strain virus. The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation.

1.1.67. Afzal, M.A., Minor, P.D., Schild, G.C. "Clinical safety issues of measles, mumps and rubella vaccines." *Bull World Health Organ* 2000;78(2):199-204. Publication Types: Review, Review, Tutorial.

Division of Virology, National Institute for Biological Standards and Control, Hertfordshire, England. mafzal@nibsc.ac.uk

The clinical safety of measles and measles-mumps-rubella vaccines has been questioned in recent reports that propose a possible link between measles virus or measles vaccines and the occurrence of juvenile Crohn disease and autism. This article reviews the outcomes of several laboratory investigations which were carried out independently to identify the presence or absence of measles virus in the intestinal tissues derived from cases of inflammatory bowel disease. One research group reported the presence of measles virus particles and genomic RNA in inflammatory bowel disease tissues, but this could not be confirmed by other groups, despite use of techniques that are highly specific and sensitive for the detection of measles virus nucleic acid in clinical specimens down to the molecular level. Based on the published data reviewed here, it can be concluded that there is no direct association between measles virus or measles vaccines and the development of Crohn disease, a conclusion which is supported by most epidemiological findings.

1.1.68. Croonenberghs, J., Delmeire, L., Verkerk, R., Lin, A.H., Meskal, A., Neels, H., Van der Planken, M., Scharpe, S., Deboutte, D., Pison, G., Maes, M. "Peripheral markers of serotonergic and noradrenergic function in post-pubertal, caucasian males with autistic disorder." *Neuropsychopharmacology* 2000 Mar;22(3):275-83.

University Center of Child and Adolescent Psychiatry, A.Z.M., Antwerp, Belgium.

Some studies have suggested that disorders in the peripheral and central metabolism of serotonin (5-HT) and noradrenaline may play a role in the pathophysiology of autistic disorder. This study examines serotonergic and noradrenergic markers in a study group of 13 male, post-pubertal, caucasian autistic patients (age 12-18 y; I.Q. > 55) and 13 matched volunteers. [3H]-paroxetine binding Kd values were significantly higher in patients with autism than in healthy volunteers. Plasma concentrations of tryptophan, the precursor of 5-HT, were significantly lower in autistic patients than in healthy volunteers. There were no significant differences between autistic and normal children in the serum concentrations of 5-HT, or the 24-hr urinary excretion of 5-hydroxy-indoleacetic acid (5-HIAA), adrenaline, noradrenaline, and dopamine. There were no significant differences in [3H]-rauwolscine binding Bmax or Kd values, or in the serum concentrations of tyrosine, the precursor of noradrenaline, between both study groups. There were highly significant positive correlations between age and 24-hr urinary excretion of 5-HIAA and serum tryptophan. The results suggest that: 1) serotonergic disturbances, such as defects in the 5-HT transporter system and lowered plasma tryptophan, may play a role in the pathophysiology of autism; 2) autism is not associated with alterations in the noradrenergic system; and 3) the metabolism of serotonin in humans undergoes significant changes between the ages of 12 and 18 years.

1.1.69. Persico, A.M., Militerni, R., Bravaccio, C., Schneider, C., Melmed, R., Conciatori, M., Damiani, V., Baldi, A., Keller, F. "Lack of association between serotonin transporter gene promoter variants and autistic disorder in two ethnically distinct samples." *Am J Med Genet* 2000 Feb 7;96(1):123-7.

Laboratory of Neuroscience, Department of Physiology and Neuroscience, Libera Università 'Campus Bio-Medico,' Rome, Italy.

Family-based studies performed to date provide conflicting evidence of linkage/association between autistic disorder and either the "short" [Cook et al., 1997: *Mol Psychiatry* 2:247-250] or the "long" [Klauck et al., 1997: *Hum Mol Genet* 6:2233-2238] allele of a polymorphic repeat located in the serotonin transporter (5-HTT) gene promoter region, affecting 5-HTT gene expression [Lesch et al., 1996: *Science* 274:1527-1531]. The present study was designed to assess linkage and linkage disequilibrium in two new ethnically distinct samples of families with primary autistic probands. The 5-HTT promoter repeat was genotyped in 54 singleton families collected in Italy and in 32 singleton and 5 multiplex families collected in the U.S.A., yielding a total sample of 98 trios. Linkage/association between 5-HTT gene promoter alleles and autistic disorder was assessed using the transmission/disequilibrium test (TDT) and the haplotype-based haplotype relative risk (HHRR). Both the Italian and the American samples, either singly or combined, displayed no evidence of linkage/association between 5-HTT gene promoter alleles and autistic disorder. Our findings do not support prominent contributions of 5-HTT gene variants to the pathogenesis of idiopathic infantile autism. Heterogeneity in pathogenetic mechanisms underlying the disease may require that linkage/association studies be targeted toward patient subgroups isolated on the basis of specific biochemical markers, such as serotonin (5-HT) blood levels. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:123-127, 2000. Copyright 2000 Wiley-Liss, Inc.

1.1.70. Christiansen, A.S. "Persisting motor control problems in 11- to 12-year-old boys previously diagnosed with deficits in attention, motor control and perception (DAMP)." *Dev Med Child Neurol* 2000 Jan;42(1):4-7.

Institute for Health Science, University of Aarhus and Solbakken, Denmark.

The aim of this study was to examine whether boys who had been previously diagnosed between the ages of 5 and 8 years with deficits in attention, motor control and perception (DAMP) still have problems with motor control, which influence their spare-time and everyday activities, at 11 to 12 years. The study comprised a well defined cohort of 10 boys with DAMP and a control group of 20 boys without DAMP matched for age, height, and weight. The Movement Assessment Battery for Children was used to assess motor control in ability to perform everyday activities, and the spare-time activities in which the boys participated were recorded. Individually, the boys previously diagnosed with DAMP had a markedly higher total score (poor performance) than the boys without DAMP ($P < 0.001$). The everyday activities of boys with DAMP were significantly affected, and they chose to participate in different sports from the control boys, i.e. none

participated in team sports. The present study does not support the concept of improvements in motor control with age in children with DAMP.

1.1.71. Hollander, E., Novotny, S., Allen, A., Aronowitz, B., Cartwright, C., DeCaria, C. "The relationship between repetitive behaviors and growth hormone response to sumatriptan challenge in adult autistic disorder." *Neuropsychopharmacology* 2000 Feb;22(2):163-7. Publication Types: Clinical Trial, Randomized Controlled Trial.

Seaver Autism Research Center, Mt. Sinai School of Medicine, New York, NY 10029, USA.

Autism is heterogeneous with respect to clinical symptoms and etiology. To sort out this heterogeneity in autism, we investigated whether specific neurobiological markers vary in parallel to core symptomatology. Specifically, we assessed growth hormone response to the 5-HT 1d agonist, sumatriptan, and linked this measure of serotonergic function to the severity of repetitive behaviors in adult autistic patients. Eleven adult patients with autism or Asperger's disorder were randomized to single dose sumatriptan (6 mg SQ) and placebo challenges, separated by a one-week interval. In adult autistic disorders, severity of repetitive behaviors at baseline, as measured by YBOCS-compulsion score, significantly positively correlated with both peak delta growth hormone response and area under the curve growth hormone response to sumatriptan. Thus, the severity of a specific behavioral dimension in autism (repetitive behaviors) parallels the sensitivity of the 5-HT 1d receptor, as manifest by sumatriptan elicited GH response.

1.1.72. Shoenfeld, Y., Aron-Maor, A. "Vaccination and autoimmunity-'vaccinosis': a dangerous liaison?" *J Autoimmun* 2000 Feb;14(1):1-10. Publication Types: Review, Tutorial.

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The question of a connection between vaccination and autoimmune illness (or phenomena) is surrounded by controversy. A heated debate is going on regarding the causality between vaccines, such as measles and anti-hepatitis B virus (HBV), and multiple sclerosis (MS). Brain antibodies as well as clinical symptoms have been found in patients vaccinated against those diseases. Other autoimmune illnesses have been associated with vaccinations. Tetanus toxoid, influenza vaccines, polio vaccine, and others, have been related to phenomena ranging from autoantibodies production to full-blown illness (such as rheumatoid arthritis (RA)). Conflicting data exists regarding also the connection between autism and vaccination with measles vaccine. So far only one controlled study of an experimental animal model has been published, in which the possible causal relation between vaccines and autoimmune findings has been examined: in healthy puppies immunized with a variety of commonly given vaccines, a variety of autoantibodies have been documented but no frank autoimmune illness was recorded. The findings could also represent a polyclonal activation (adjuvant reaction). The mechanism (or mechanisms) of autoimmune reactions

following immunization has not yet been elucidated. One of the possibilities is molecular mimicry; when a structural similarity exists between some viral antigen (or other component of the vaccine) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Other possible mechanisms are discussed. Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunization (e.g. Guillain-Barre syndrome). The issue of the risk of vaccination remains a philosophical one, since to date the advantages of this policy have not been refuted, while the risk for autoimmune disease has not been irrevocably proved. We discuss the pros and cons of this issue (although the temporal relationship (i.e. always 2-3 months following immunization) is impressive). Copyright 2000 Academic Press.

1.1.73. Grimbacher, B., Dutra, A.S., Holland, S.M., Fischer, R.E., Pao, M., Gallin, J.L., Puck, J.M. **"Analphoid marker chromosome in a patient with hyper-IgE syndrome, autism, and mild mental retardation."** *Genet Med* 1999 Jul-Aug;1(5):213-8.

Genetics and Molecular Biology Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-4442, USA.

Hyper-IgE syndrome with recurrent infections (HIES) is a primary immunodeficiency disease characterized by recurrent skin and lung abscesses and extreme elevations of serum IgE, but also involving dentition, bones, and connective tissue. Although the etiology of HIES is unknown, autosomal dominant inheritance has been observed in multiple kindreds. A 17 year old male with sporadic HIES, autism, and mild mental retardation was found to have a supernumerary marker chromosome in peripheral blood lymphocytes and skin fibroblasts. Microdissection and FISH analysis of the marker chromosome showed that it was derived from a small interstitial deletion of one homologue of chromosome 4q21. Lack of hybridization of probes specific for telomeres and alphoid centromeres, including a centromere 4 specific probe, established that the marker was an alphoid ring chromosome. Comparative genotyping of transformed B-cell subclones with (M+) and without (M-) the marker chromosome showed loss of the maternal alleles in M- cells between markers D4S1569 and D4S3010. FISH using YAC clones from 4q21 confirmed the size and location of the interstitial deletion. Thus our patient's phenotypes were associated with de novo formation of a marker chromosome containing 15-20 cM of DNA deleted from his maternally derived chromosome 4. Proximal chromosome 4q therefore is a candidate region for disease genes for both HIES and autism. Identification of genes disrupted or lost during the formation of the marker chromosome as well as linkage studies in kindreds with HIES or autism may help us to understand the etiology of these complex phenotypes.

1.1.74. Burd, L., Severud, R., Kerbeshian, J., Klug, M.G. **"Prenatal and perinatal risk factors for autism."** *J Perinat Med* 1999;27(6):441-50.

University of North Dakota School of Medicine and Health Sciences, North Dakota Fetal Alcohol Syndrome Center, Grand Forks, USA. laburd@mail.med.und.nodak.edu.

AIM: To identify pre- and perinatal risk factors for autism. METHOD: Case control study. We matched names of patients from North Dakota who met DSM criteria for autism, a pervasive developmental disorder, and autistic disorder with their birth certificates. Five matched controls were selected for each case. RESULTS: Univariate analysis of the 78 cases and 390 controls identified seven risk factors. Logistic modeling to control for confounding produced a five variable model. The model parameters were $\chi^2 = 36.6$ and $p < 0.001$. The five variables in the model were decreased birth weight, low maternal education, later start of prenatal care, and having a previous termination of pregnancy. Increasing father's age was associated with increased risk of autism. CONCLUSION: This methodology may provide an inexpensive method for clinics and public health providers to identify risk factors and to identify maternal characteristics of patients with mental illness and developmental disorders.

1.1.75. Kohler, M., Assmann, B., Brautigam, C., Storm, W., Marie, S., Vincent, M.F., Van den Berghe, G., Simmonds, H.A., Hoffmann, G.F. **"Adenylosuccinase deficiency: possibly underdiagnosed encephalopathy with variable clinical features."** *Eur J Paediatr Neurol* 1999;3(1):3-6.

University Children's Hospital, Marburg, Germany.

Adenylosuccinase deficiency is an autosomal recessive inherited defect of purine synthesis. In enzyme deficient patients, two normally undetectable compounds, succinylaminoimidazole carboxamide riboside and succinyladenosine, accumulate in urine, cerebrospinal fluid and, to a minor extent, in plasma. Analysing 150 highly selected urine specimens from patients with unidentified neurogenerative disorders we discovered the first two German cases of adenylosuccinase deficiency. The deficiency causes moderate to severe mental retardation, often accompanied by epileptic seizures and/or autistic features, and is occasionally associated with growth retardation and muscular hypotonia. Of the two German cases we present here, one patient fits into the clinical picture outlined by previous reports. The other patient, however, shows a pattern of symptoms so far undescribed: severe early infantile epileptic encephalopathy with reduced myelination. On mutation analysis this patient is the first to reveal a 39 base pair deletion in the adenylosuccinase gene in contrast to the point mutations detected in previous cases. Adenylosuccinase deficiency may be an underdiagnosed metabolic disorder with variable expression. This should be taken into consideration in patients with unclassified neurological conditions.

1.1.76. Taylor, D.C., Neville, B.G., Cross, J.H. **"Autistic spectrum disorders in childhood epilepsy surgery candidates."** *Eur Child Adolesc Psychiatry* 1999 Sep;8(3):189-92.

Neurosciences Unit, Institute of Child Health and Great Ormond St. Hospital for Children NHS Trust, Mecklenburgh Sq., UK-London WC1 2AP.

One third of children with autistic spectrum disorders (or pervasive developmental disorders) enter that state by regression from a more normal prior development at the onset of epilepsy or epileptiform abnormality in the electroencephalogram. In a very small proportion structural lesions of the temporal lobes are discovered. These form part of the sample of children coming to a surgical treatment programme. Ninety-eight child candidates for epilepsy surgery were seen by one neuropsychiatrist. Their psychiatric diagnoses were coded on DSM IV schedules. Other variables of interest were the age at onset of epilepsy; the nature, the side, and time of acquisition of the lesion; intelligence, and sex. There were 19 children with autistic spectrum disorders including eight with Asperger's syndrome. Ten of the children in the autistic group had right brain lesions; six were dysembryoplastic neuroepithelial tumours (DNETs); two were cortical dysplasias; one tuberous sclerosis; one hemi-cortical defect; and 1 mesial temporal sclerosis. Nine started epilepsy in their first year; nine had IQs in the retarded range; nine of the 11 were male. Six of eight Asperger's children had right brain lesions; two DNETs; four mesial temporal sclerosis; one Rasmussen encephalitis. Four started epilepsy in their first year; one was retarded; five were female. Children who had no, or other, psychiatric disorder also showed "mass" lesions, or temporal sclerosis but with different biases as to side, sex, and very early onset of epilepsy from the autistic spectrum group. Very early onset of epilepsy, with lesions of embryonal origin, in the right temporal lobe, strongly predisposed males towards autistic regression. Such patients should be referred very early for consideration of urgent surgical treatment.

1.1.77. Fiumara, A., Sciotto, A., Barone, R., D'Asero, G., Munda, S., Parano, E., Pavone, L. **"Peripheral lymphocyte subsets and other immune aspects in Rett syndrome."** *Pediatr Neurol* 1999 Sep;21(3):619-21.

Department of Paediatric Neurology, Paediatric Clinic, University of Catania, Italy.

A possible role of the immune system in the pathogenesis of some neurologic disorders, including infantile autism, was recently postulated. This observation prompted the authors to investigate some immunologic aspects in a group of patients with Rett syndrome, a disorder still not completely clarified but with some points of commonality with infantile autism. Humoral and cell-mediated immunity were investigated in 20 females with Rett syndrome. Peripheral lymphocyte subsets revealed a reduced percentage of CD8+ suppressor-cytotoxic cells in all of the patients with Rett syndrome, resulting in an increased CD4+/CD8+ ratio. In addition, 15 (75%) of the 20 patients had low levels of natural killer cells. Soluble interleukin-2 receptor was elevated in the youngest patients. Antineuronal and antimyelin ganglioside antibodies were absent, as were antinuclear antibodies, antistriated muscle antibodies, and antismooth muscle antibodies. Immunoglobulin fractions and complement were normal for age in all of the patients.

1.1.78. Annett, M. **"The theory of an agnosic right shift gene in schizophrenia and autism."** *Schizophr Res* 1999 Oct 19;39(3):177-82.

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The right shift (RS) theory (Annett, M., 1972. The distribution of manual asymmetry. *Br. J. Psychol.* 63, 343-358; Annett, M., 1985. *Left, Right, Hand and Brain: The Right Shift Theory.* Lawrence Erlbaum, London) suggests that the typical pattern of human cerebral and manual asymmetries depends on a single gene (RS+) which impairs speech-related cortex of the right hemisphere. The theory offers solutions to several puzzles, including the distribution of handedness in families (Annett, M., 1978. *A Single Gene Explanation of Right and Left Handedness and Brainedness.* Lanchester Polytechnic, Coventry; Annett, M., 1996. In defense of the right shift theory. *Percept. Motor Skills* 82, 115-137), relations between handedness and cerebral speech laterality (Annett, M., 1975. Hand preference and the laterality of cerebral speech. *Cortex* 11, 305-328; Annett, M., Alexander, M.P., 1996. Atypical cerebral dominance: predictions and tests of the right shift theory. *Neuropsychologia* 34, 1215-1227) and handedness and dyslexia (Annett, M. et al., 1996. Types of dyslexia and the shift to dextrality. *J. Child Psychol. Psychiatry* 37, 167-180). If Crow's (Crow, T.J. et al., 1989. Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Arch. Gen. Psychiatry* 46, 1145-1150; Crow, T.J., 1997. Is schizophrenia the price that Homo sapiens pays for language? *Schizophr. Res.* 28, 127-141) theory that schizophrenia is due to an anomaly of cerebral dominance is correct, and if the RS theory is correct, schizophrenia could be due to an anomaly of the RS+ gene. If the RS+ gene were at risk for a mutation which caused a loss of directional coding, the mutant could be described as 'agnosic' for left and right. Such a gene would impair either hemisphere at random. When paired with another RS+ gene, both hemispheres would be impaired in 50% of cases. The other 50% and people in whom the agnosic gene is paired with an RS-allele (neutral for asymmetry and not giving hemisphere impairment) would have one unaffected hemisphere and, thus, normal development. Quantitative predictions based on the RS genetic theory as previously developed, plus an agnosic mutant with frequency required to give schizophrenia in 1% of the population, are consistent with estimates of concordance for schizophrenia in relatives. Homozygotes of the agnosic mutant would occur at about the rate estimated for autism.

1.1.79. Maestrini, E., Lai, C., Marlow, A., Matthews, N., Wallace, S., Bailey, A., Cook, E.H., Weeks, D.E., Monaco, A.P. **"Serotonin transporter (5-HTT) and gamma-aminobutyric acid receptor subunit beta3 (GABRB3) gene polymorphisms are not associated with autism in the IMGSA families. The International Molecular Genetic Study of Autism Consortium."** *Am J Med Genet* 1999 Oct 15;88(5):492-6.

The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. maestrini@well.ox.ac.uk.

Previous studies have suggested that the serotonin transporter (5-HTT) gene and the gamma-aminobutyric acid receptor subunit beta3 (GABRB3) gene, or other genes in the 15q11-q13 region, are possibly involved in susceptibility to autism.

To test this hypothesis we performed an association study on the collection of families from the International Molecular Genetic Study of Autism (IMGSA) Consortium, using the transmission disequilibrium test. Two polymorphisms in the 5-HTT gene (a functional insertion-deletion polymorphism in the promoter and a variable number tandem repeat in the second intron) were examined in 90 families comprising 174 affected individuals. Furthermore, seven microsatellite markers spanning the 15q11-q13 region were studied in 94 families with 182 affected individuals. No significant evidence of association or linkage was found at any of the markers tested, indicating that the 5-HTT and the GABRB3 genes are unlikely to play a major role in the aetiology of autism in our family data set.

1.1.80. Alberti, A., Pirrone, P., Elia, M., Waring, R.H., Romano, C. "Sulphation deficit in "low-functioning" autistic children: a pilot study." *Biol Psychiatry* 1999 Aug 1;46(3):420-4.

Department of Pediatrics, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy.

BACKGROUND: Parents of autistic children and autism support groups often report that autistic episodes are exacerbated when the children eat certain foodstuffs such as dairy products, chocolates, wheat, corn sugar, apples, and bananas. The hypothesis that autistic behavior might be related to metabolic dysfunctions has led us to investigate in a group of "low functioning" autistic children and in an age-matched control group each made up of 20 subjects, the sulphation capacity available. **METHODS:** Utilizing the biochemical characteristics of paracetamol we evaluated by high performance liquid chromatography, the urine paracetamol-sulfate/paracetamol-glucuronide (PS/PG) ratio in all subjects following administration of this drug. **RESULTS:** The PS/PG ratio in the group of autistic subjects gave a significantly lower results than the control group with $p < .00002$. **CONCLUSIONS:** The inability to effectively metabolize certain compounds particularly phenolic amines, toxic for the CNS, could exacerbate the wide spectrum of autistic behavior.

1.1.81. Pedersen, O.S., Liu, Y., Reichelt, K.L. "Serotonin uptake stimulating peptide found in plasma of normal individuals and in some autistic urines." *J Pept Res* 1999 Jun;53(6):641-6.

Research Institute, University of Oslo, Rikshospitalet, Norway.

We have isolated a tripeptide from normal plasma and autistic urines which stimulates the uptake of serotonin (5-HT) into platelets. This peptide was purified by high-performance liquid chromatography (HPLC) and characterized by sequencing and mass-spectrometry. Synthetic peptide showed co-chromatography with the biological sample in the HPLC systems used. Close to 60% of the autistic children diagnosed using the Diagnostic Statistical Manual III-R had an increased HPLC peak eluting like this peptide in their urines compared with controls.

1.1.82. Taylor, B., Miller, E., Farrington, C.P., Petropoulos, M.C., Favot-Mayaud, I., Li, J., Waight, P.A. "Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association." *Lancet* 1999 Jun 12;353(9169):2026-9.

Department of Community Child Health, Royal Free and University College Medical School, University College London, UK.

BACKGROUND: We undertook an epidemiological study to investigate whether measles, mumps, and rubella (MMR) vaccine may be causally associated with autism. **METHODS:** Children with autism born since 1979 were identified from special needs/disability registers and special schools in eight North Thames health districts, UK. Information from clinical records was linked to immunisation data held on the child health computing system. We looked for evidence of a change in trend in incidence or age at diagnosis associated with the introduction of MMR vaccination to the UK in 1988. Clustering of onsets within defined postvaccination periods was investigated by the case-series method. **FINDINGS:** We identified 498 cases of autism (261 of core autism, 166 of atypical autism, and 71 of Asperger's syndrome). In 293 cases the diagnosis could be confirmed by the criteria of the International Classification of Diseases, tenth revision (ICD10: 214 [82%] core autism, 52 [31%] atypical autism, 27 [38%] Asperger's syndrome). There was a steady increase in cases by year of birth with no sudden "step-up" or change in the trend line after the introduction of MMR vaccination. There was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated. There was no temporal association between onset of autism within 1 or 2 years after vaccination with MMR (relative incidence compared with control period 0.94 [95% CI 0.60-1.47] and 1.09 [0.79-1.52]). Developmental regression was not clustered in the months after vaccination (relative incidence within 2 months and 4 months after MMR vaccination 0.92 [0.38-2.21] and 1.00 [0.52-1.95]). No significant temporal clustering for age at onset of parental concern was seen for cases of core autism or atypical autism with the exception of a single interval within 6 months of MMR vaccination. This appeared to be an artifact related to the difficulty of defining precisely the onset of symptoms in this disorder. **INTERPRETATION:** Our analyses do not support a causal association between MMR vaccine and autism. If such an association occurs, it is so rare that it could not be identified in this large regional sample.

1.1.83. Riikonen, R., Vanhala, R. "Levels of cerebrospinal fluid nerve-growth factor differ in infantile autism and Rett syndrome." *Dev Med Child Neurol* 1999 Mar;41(3):148-52.

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Autism and Rett syndrome (RS) are both developmental disorders of unknown origin. Autism is a behaviourally defined syndrome. RS, which affects girls only, is characterized by a profound learning disability following early normal development, with a consistent cluster of clinical

features. Differentiation of RS from infantile autism in the very early stages of the disorders is not always easy. Both syndromes still lack discriminative laboratory markers for accurate diagnosis and differentiation. We decided to compare the CSF nerve-growth factor (NGF) levels of children with infantile autism and children with RS using enzyme-linked immunosorbent assay (ELISA). Our findings of mainly normal CSF NGF in autism and low to negligible values in RS are in agreement with the different morphological and neurochemical findings (brain growth, affected brain areas, neurotransmitter metabolism) in the two syndromes. CSF NGF could be used as a biochemical marker for differentiation of patients with autism from those with RS.

1.1.84. Insel, T.R., O'Brien, D.J., Leckman, J.F. "Oxytocin, vasopressin, and autism: is there a connection?" *Biol Psychiatry* 1999 Jan 15;45(2):145-57. Publication Types: Review, Review, Tutorial.

Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia 30322, USA.

Autism is a poorly understood developmental disorder characterized by social impairment, communication deficits, and compulsive behavior. The authors review evidence from animal studies demonstrating that the nonapeptides, oxytocin and vasopressin, have unique effects on the normal expression of species-typical social behavior, communication, and rituals. Based on this evidence, they hypothesize that an abnormality in oxytocin or vasopressin neurotransmission may account for several features of autism. As autism appears to be a genetic disorder, mutations in the various peptide, peptide receptor, or lineage-specific developmental genes could lead to altered oxytocin or vasopressin neurotransmission. Many of these genes have been cloned and sequenced, and several polymorphisms have been identified. Recent gene targeting studies that alter expression of either the peptides or their receptors in the rodent brain partially support the autism hypothesis. While previous experience suggests caution in hypothesizing a cause or suggesting a treatment for autism, the available preclinical evidence with oxytocin and vasopressin recommends the need for clinical studies using gene scanning, pharmacological and neurobiological approaches.

1.1.85. Bolte, E.R. "Autism and *Clostridium tetani*." *Med Hypotheses* 1998 Aug;51(2):133-44. Publication Types: Review, Review, Tutorial.

Autism is a severe developmental disability believed to have multiple etiologies. This paper outlines the possibility of a subacute, chronic tetanus infection of the intestinal tract as the underlying cause for symptoms of autism observed in some individuals. A significant percentage of individuals with autism have a history of extensive antibiotic use. Oral antibiotics significantly disrupt protective intestinal microbiota, creating a favorable environment for colonization by opportunistic pathogens. *Clostridium tetani* is an ubiquitous anaerobic bacillus that produces a potent neurotoxin. Intestinal colonization by *C. tetani*, and subsequent neurotoxin release, have been demonstrated in

laboratory animals which were fed vegetative cells. The vagus nerve is capable of transporting tetanus neurotoxin (TeNT) and provides a route of ascent from the intestinal tract to the CNS. This route bypasses TeNT's normal preferential binding sites in the spinal cord, and therefore the symptoms of a typical tetanus infection are not evident. Once in the brain, TeNT disrupts the release of neurotransmitters by the proteolytic cleavage of synaptobrevin, a synaptic vesicle membrane protein. This inhibition of neurotransmitter release would explain a wide variety of behavioral deficits apparent in autism. Lab animals injected in the brain with TeNT have exhibited many of these behaviors. Some children with autism have also shown a significant reduction in stereotyped behaviors when treated with antimicrobials effective against intestinal clostridia. When viewed as sequelae to a subacute, chronic tetanus infection, many of the puzzling abnormalities of autism have a logical basis. A review of atypical tetanus cases, and strategies to test the validity of this paper's hypothesis, are included.

1.1.86. Duclos, P., Ward, B.J. "Measles vaccines: a review of adverse events." *Drug Saf* 1998 Dec;19(6):435-54. Publication Types: Review, Review Literature.

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A great deal of controversy has recently been generated over the publication of several articles implicating measles vaccine in the induction of Crohn's disease and autism. The publication of this work has already had a negative impact on measles vaccine acceptance in the UK. These allegations are particularly troubling because they arise in the context of increased use of measles vaccine as global control of measles nears and the international community considers strategies for a drive towards eradication. In 1994, the US Institute of Medicine reviewed the world literature and published a comprehensive review of adverse events associated with measles-containing vaccines. Reviewing the literature published between 1994 and the present day, reveals that there is considerable new data suggesting that modified gelatin rather than egg proteins is responsible for most episodes of anaphylaxis following measles vaccination. New work weakens the possible links between measles vaccine and subacute sclerosing panencephalitis and Guillain-Barre syndrome, but strengthens the rare association of measles-containing vaccines with post infectious encephalomyelitis. The alleged associations between measles vaccination and Crohn's disease and autism are based upon weak science and have largely been refuted by a large volume of stronger work. A review of the data generated in the last 4 years amply demonstrates the continued efforts of the scientific community to monitor and understand true measles vaccine-associated adverse events. The rapidity and clarity of this same community's debunking of the spurious associations with Crohn's disease and autism suggests that those charged with vaccination programmes have learned from past mistakes. During 30 years of worldwide use, measles vaccination has proven to be one of the safest and most successful health

interventions in the history of mankind. It is not a 'perfect' vaccine, but the benefits of measles vaccination far outweigh the risks even in countries with low incidence of measles and high rates of measles vaccine coverage.

1.1.87. Dawson, G., Meltzoff, A.N., Osterling, J., Rinaldi, J. "Neuropsychological correlates of early symptoms of autism." *Child Dev* 1998 Oct;69(5):1276-85.

Department of Psychology, University of Washington, Seattle 98195, USA.

Both the medial temporal lobe and dorsolateral prefrontal cortex have been implicated in autism. In the present study, performance on two neuropsychological tasks—one tapping the medial temporal lobe and related limbic structures, and another tapping the dorsolateral prefrontal cortex—was examined in relation to performance on tasks assessing autistic symptoms in young children with autism, and developmentally matched groups of children with Down syndrome or typical development. Autistic symptoms included orienting to social stimuli, immediate and deferred motor imitation, shared attention, responses to emotional stimuli, and symbolic play. Compared with children with Down syndrome and typically developing children, children with autism performed significantly worse on both the medial temporal lobe and dorsolateral prefrontal tasks, and on tasks assessing symptoms domains. For children with autism, the severity of autistic symptoms was strongly and consistently correlated with performance on the medial temporal lobe task, but not the dorsolateral prefrontal task. The hypothesis that autism is related to dysfunction of the medial temporal lobe and related limbic structures, such as the orbital prefrontal cortex, is discussed.

1.1.88. Smalley, S.L. "Autism and tuberous sclerosis." *J Autism Dev Disord* 1998 Oct;28(5):407-14. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, University of California-Los Angeles-School of Medicine 90024, USA.

Autism and pervasive developmental disorders (PDD) are common in tuberous sclerosis (TSC). The frequency of autism is about 25%, with 40-45% of TSC cases meeting criteria for autism or PDD. Among autistic populations, the frequency of TSC is 1-4% and perhaps as high as 8-14% among the subgroup of autistic individuals with a seizure disorder. Mental retardation (MR) and seizures, particularly infantile spasms, are significant risk factors in the development of autism/PDD in TSC; however, neither are sufficient or necessary for the development of these behaviors. The mechanism underlying the association of autism and TSC is as yet unclear but clinical features and neuroimaging investigations suggest that an abnormal TSC gene may directly influence the development of autism rather than it being a secondary effect of seizures or MR. The presence of autism/PDD may arise if the TSC gene mutations occur at critical stages of neural development in neural tissue of brain regions critical in the development of autism.

1.1.89. Fischer, K.M. "Expanded (CAG)_n, (CGG)_n and (GAA)_n trinucleotide repeat microsatellites, and mutant purine synthesis and pigmentation genes cause schizophrenia and autism." *Med Hypotheses* 1998 Sep;51(3):223-33. Publication Types: Review, Review, Tutorial.

Unstable (CAG)_n trinucleotide repeat microsatellites are hypothesized to cause schizophrenia. The (CAG)_n microsatellite of dominant spinal cerebellar ataxia type 1 (SCA1) is a candidate schizophrenia gene. Autism results from expansions of (CGG)_n and (GAA)_n trinucleotide repeat stretches at fragile X syndrome (FRAXA), and the recessive Friedreich's ataxia (FA). Dominant ataxia genes may cause schizophrenia and recessive ataxia genes may cause autism. Syndromes with autism show purine synthesis defects (PSDs) and/or pigmentation defects (PDs). Autism is caused by very lengthy expansions of (CAG)_n, (CGG)_n and (GAA)_n repeats, while schizophrenia results from much smaller (CAG)_n and (CGG)_n repeat expansions.

1.1.90. Miller, M.T., Stromland, K., Gillberg, C., Johansson, M., Nilsson, E.W. "The puzzle of autism: an ophthalmologic contribution." *Trans Am Ophthalmol Soc* 1998;96:369-85; discussion 385-7.

University of Illinois at Chicago, Department of Ophthalmology, USA.

PURPOSE: A previous study of 86 thalidomide-affected subjects with ophthalmic manifestations revealed the unexpected finding of autism in 4 of the 5 severely retarded individuals. The subjects had anomalies associated with an early gestational effect of thalidomide, including facial nerve palsy and incomitant strabismus. Because autism has been observed in a few cases of Mobius sequence (Mobius syndrome), a condition characterized by involvement of the sixth and seventh cranial nerves, the similarity to early thalidomide embryopathy suggested a relation between cranial nerve involvement and autism. The present study was undertaken to further evaluate the association of autism with patients manifesting findings of Mobius syndrome. **METHODS:** A prospective study of 25 Swedish patients with Mobius sequence was conducted. The patients had a complete multidisciplinary evaluation, including ophthalmologic and psychiatric examinations and standard testing for autism. Findings associated with autism were compared with the ocular and systemic anomalies of the 4 thalidomide-affected subjects. **RESULTS:** In the Mobius group 6 patients had autism, achieving the criteria for autism according to all the diagnostic manuals that were used. One patient showed autistic-like conditions meeting fewer numbers of the criteria. A few were too young to be meeting evaluated. Incomitant strabismus ranging from primary abduction defects alone to a horizontal gaze paresis pattern was noted in these patients, in addition to characteristic findings of seventh nerve paresis. Aberrant lacrimation was observed in many cases, especially often associated with autism. **CONCLUSION:** The common group of anomalies noted in both cases of thalidomide embryopathy and Mobius sequence suggests that brain-stem damage probably early in embryogenesis can sometimes be associated with autism.

ETIOLOGY

Psychosocial

1.2.1. Goldman, L.R., Koduru, S. **“Chemicals in the environment and developmental toxicity to children: a public health and policy perspective.”** *Environ Health Perspect* 2000 Jun;108 Suppl 3:443-8.

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There are numerous pesticides and toxic chemicals in the environment that have yet to be evaluated for potential to cause developmental neurotoxicity. Recent legislation and testing initiatives provide an impetus to generating more information about potential hazards to children. In the United States, the 1996 Food Quality Protection Act (FQPA) required the U.S. Environmental Protection Agency (U.S. EPA) to make a finding that a pesticide food use is safe for children. In addition, the law requires U.S. EPA to incorporate an additional 10-fold factor in risk assessments for pesticide residue tolerances to take into account the special sensitivities of infants and children as well as incomplete data with respect to toxicity and exposures. The potential of chemicals in food and drinking water to cause endocrine disruption will also be examined via the Endocrine Disruptor Screening and Testing Program required by the FQPA and the 1996 Safe Drinking Water Act. In addition, a new voluntary chemical information program will provide screening-level information for the some 2,800 high-volume chemicals in commerce in the United States. These initiatives will need to be accompanied by research focused on developmental toxicity for children, including developmental disabilities. Developmental disabilities exact a large toll on children's health in the United States. Three major developmental disabilities—autism, cerebral palsy, and severe mental retardation—each affect substantial numbers of children. We know very little about the etiology of these conditions. A number of priority areas for research are suggested, including a large environmental prospective study of developmental neurotoxicity.

1.2.2. London, E.A. **“The environment as an etiologic factor in autism: a new direction for research.”** *Environ Health Perspect* 2000 Jun;108 Suppl 3:401-4. Publication Types: Review, Review, Tutorial.

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Autism is one of a group of developmental disorders that have devastating lifelong effects on its victims. Despite the severity of the disease and the fact that it is relatively common (15 in 10,000), there is still little understanding of its etiology. Although believed to be highly genetic, no abnormal genes have been found. Recent findings in autism and in related disorders point to the possibility that the disease is caused by a gene-environment interaction. Epidemiologic studies indicate that the number of cases of autism is increasing dramatically each year. It is not clear whether this is due to a real increase in the disease or whether this is an artifact of ascertainment. A new theory regarding the etiology of autism suggests that it may be a disease of very early fetal development (approximately day 20-24 of gestation). This

theory has initiated new lines of investigation into developmental genes. Environmental exposures during pregnancy could cause or contribute to autism based on the neurobiology of these genes.

1.2.3. Weiss, B., Landrigan, P.J. **“The developing brain and the environment: an introduction.”** *Environ Health Perspect* 2000 Jun;108 Suppl 3:373-4.

Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA.

mental retardation: timing and thresholds; (italic)b(/italic)) endocrine dysfunction and developmental disabilities: dose and target implications; (italic)c(/italic)) attention-deficit disorder-ADHD and learning disabilities; and (italic)d(/italic)) new horizons: extending the boundaries. Support for the Rochester conference came from both public and private sources. The National Institute of Environmental Health Sciences (NIEHS), the National Institute of Child Health and Human Development, and the EPA represented the federal government. The conference also received grants from several foundations: the Jennifer Altman Foundation, the Heinz Family Foundation, the National Alliance for Autism Research, the Violence Research Foundation, the Wacker Foundation, and the Winslow Foundation. The second of these conferences helped launch a new Center for Children's Health and the Environment at the Mount Sinai School of Medicine. It was held in New York City on 24-25 May 1999, and was convened specifically to consider the intersection between neurodevelopmental impairment, environmental chemicals, and prevention. Over 300 health scientists, pediatricians, and public health professionals examined the growing body of evidence linking environmental toxins to neurobehavioral disorders. The conference title was Environmental Influences on Children: Brain, Development, and Behavior. The conference began by reviewing well-known examples of deleterious effects of environmental chemicals, including lead and PCBs, on children's brains. The conferees then considered the potential impact of environmental chemicals on neurological disorders with particular focus on ADHD, autism, and Parkinson's disease. The inclusion of Parkinson's disease was intended to signal the notion that exposures in early life may have an influence on the evolution of neurological disease in later life. Support for the Mount Sinai conference came from the Superfund Basic Research Program (NIEHS); The Pew Charitable Trusts; the Institute for Health and the Environment at the University of Albany School of Public Health; the Agency for Toxic Substances and Disease Research (ATSDR); the Ambulatory Pediatric Association; Myron A. Mehlman, PhD; the National Center for Environmental Assessment (EPA); the National Center for Environmental Health (CDC); the National Institute of Child Health and Human Development; the Office of Children's Health Protection (EPA); Physicians for Social Responsibility; The New York Academy of Medicine; The New York Community Trust; and the Wallace Genetic Foundation. The impact of environmental toxins on children's health has become a topic of major concern in the federal government.

Eight new research centers in children's environmental health have been established in the past 2 years with joint funding from EPA and NIEHS. Clinical units that specialize in the treatment of children with environmentally induced illness have been developed across the nation with grant support from ATSDR. The American Academy of Pediatrics has just published its *Handbook of Pediatric Environmental Health*, the "Green Book," which is available to pediatricians throughout the Americas. Children's environmental health has climbed to a critical position as we launch the new millennium. This monograph marks a significant milestone in the evolution of this emerging discipline.

1.2.4. Landau, E.C., Cicchetti, D.V., Klin, A., Volkmar, F.R. "Season of birth in autism: a fiction revisited." *J Autism Dev Disord* 1999 Oct;29(5):385-93.

Bar Ilan University, Ramat Gan, Israel.

Variations of season of birth among autistic individuals were studied. The replicability of previously reported increases in birth rates in the months of March and August were examined in groups of individuals with autism or mental retardation (the comparison group). The sample was obtained from the Yale Child Study Center Developmental Disabilities Clinic and from the DSM-IV Autism/PDD field trial. Data were analyzed by applying the Jonckheere test of ordinal trend and

the chi-square test, with Yates correction factor. With respect to March and August births, and with calculations based on the beginning and middle of the month, no significant seasonal effect was observed. Samples were subcategorized into verbal and mute groups, and again results failed to support the seasonality hypothesis.

1.2.5. Maestro, S., Casella, C., Milone, A., Muratori, F., Palacio-Espasa, F. "Study of the onset of autism through home movies." *Psychopathology* 1999 Nov-Dec;32(6):292-300.

IRCCS Stella Maris, University of Pisa, Italy.

The authors describe the natural history and the beginning of pervasive developmental disorders (PDD) by the observation of home movies. The sample is composed of 26 children aged 18 months to 5 or 6 years at the first consultation. The methodology used in the observation of home movies includes: (1) application of the ERC-A-III scale for recognizing the precocious symptoms of autism; (2) analysis of the coming out and coming off of social, emotional and cognitive competences. The authors, starting from the analysis of these data, describe three kinds of onset and courses of PDD: progressive, regressive and fluctuating. The authors present some conclusive considerations on the different age of PDD onset in home movies, in anamnestic reconstruction and in recall for diagnosis.

ETIOLOGY

Genetics

1.3.1. Wilcox, J.A., Tsuang, M.T., Schnurr, T., Baida-Fragoso, N. "Case-control family study of lesser variant traits in autism." *Neuropsychobiology*. 2003;47(4):171-7.

Department of Psychiatry, Texas Tech University Health Sciences Center, 4800 Alberta Avenue, El Paso, TX 79905, USA. james.wilcox@ttuhsc.edu

Family data were obtained from the relatives of 30 autistic patients, 30 patients with other pervasive developmental disorder and 30 healthy controls. Detailed interviewing was conducted to document any evidence of psychiatric illness of the family members of these probands. Anxiety disorders and obsessive-compulsive illness stood out as being closely associated with having autistic individuals in the family. The findings suggest that autism is a spectrum disorder that may be associated with anxiety and obsessive-compulsive illness. This type of association is consistent with a polygenic threshold effect for this group of conditions.

1.3.2. Nurmi, E.L., Dowd, M., Tadevosyan-Leyfer, O., Haines, J.L., Folstein, S.E., Sutcliffe, J.S. "Exploratory subsetting of autism families based on savant skills improves evidence of genetic linkage to 15q11-q13." *J Am Acad Child Adolesc Psychiatry*. 2003 Jul;42(7):856-63.

Medical Scientist Training Program, Vanderbilt University, Nashville, TN 37232-0615, USA.

OBJECTIVE: Autism displays a remarkably high heritability but a complex genetic etiology. One approach to identifying susceptibility loci under these conditions is to define more homogeneous subsets of families on the basis of genetically relevant phenotypic or biological characteristics that vary from case to case. **METHOD:** The authors performed a principal components analysis, using items from the Autism Diagnostic Interview, which resulted in six clusters of variables, five of which showed significant sib-sib correlation. The utility of these phenotypic subsets was tested in an exploratory genetic analysis of the autism candidate region on chromosome 15q11-q13. **RESULTS:** When the Collaborative Linkage Study of Autism sample was divided, on the basis of mean proband score for the "savant skills" cluster, the heterogeneity logarithm of the odds under a recessive model at D15S511, within the GABRB3 gene, increased from 0.6 to 2.6 in the subset of families in which probands had greater savant skills. **CONCLUSIONS:** These data are consistent with the genetic contribution of a 15q locus to autism susceptibility in a subset of affected individuals exhibiting savant skills. Similar types of skills have been noted in individuals with Prader-Willi syndrome, which results from deletions of this chromosomal region.

1.3.3. Kaminen, N., Hannula-Jouppi, K., Kestila, M., Lahermo, P., Muller, K., Kaaranen, M., Myllyluoma, B., Voutilainen, A., Lyytinen, H., Nopola-Hemmi, J., Kere, J. "A genome scan for developmental dyslexia confirms linkage to chromosome 2p11 and suggests a new locus on 7q32." *J Med Genet*. 2003 May;40(5):340-5.

Department of Medical Genetics, Biomedicum, University of Helsinki, Finland.

Developmental dyslexia is a distinct learning disability with unexpected difficulty in learning to read despite adequate intelligence, education, and environment, and normal senses. The genetic aetiology of dyslexia is heterogeneous and loci on chromosomes 2, 3, 6, 15, and 18 have been repeatedly linked to it. We have conducted a genome scan with 376 markers in 11 families with 38 dyslexic subjects ascertained in Finland. Linkage of dyslexia to the vicinity of DYX3 on 2p was confirmed with a non-parametric linkage (NPL) score of 2.55 and a lod score of 3.01 for a dominant model, and a novel locus on 7q32 close to the SPCH1 locus was suggested with an NPL score of 2.77. The SPCH1 locus has previously been linked with a severe speech and language disorder and autism, and a mutation in exon 14 of the FOXP2 gene on 7q32 has been identified in one large pedigree. Because the language disorder associated with the SPCH1 locus has some overlap with the language deficits observed in dyslexia, we sequenced the coding region of FOXP2 as a candidate gene for our observed linkage in six dyslexic subjects. No mutations were identified. We conclude that DYX3 appears to be important for dyslexia susceptibility in many Finnish families, and a suggested linkage of dyslexia to chromosome 7q32 will need verification in other data sets.

1.3.4. Gallagher, L., Becker, K., Kearney, G., Dunlop, A., Stallings, R., Green, A., Fitzgerald, M., Gill, M. "Brief report: A case of autism associated with del(2)(q32.1q32.2) or (q32.2q32.3)." *J Autism Dev Disord*. 2003 Feb;33(1):105-8.

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Autism is a neurodevelopmental disorder presenting in the first 3 years of life. Deficits occur in the three core areas of communication, social interaction, and behavior. The causes of autism are unknown, but clinical genetic studies show strong evidence in favor of a genetic etiology. Molecular genetic studies report some association with candidate genes, and candidate regions have emerged from several genome-wide linkage studies. Here we report a clinical case of autism with a deletion on chromosome 2 in a young male with high-functioning autism. The deletion seems to correspond with regions emerging from linkage studies. We propose this as a possible candidate region in the search for autism genes.

1.3.5. Ogdie, M.N., Macphie, I.L., Minassian, S.L., Yang, M., Fisher, S.E., Francks, C., Cantor, R.M., McCracken, J.T., McGough, J.J., Nelson, S.F., Monaco, A.P., Smalley, S.L. "extended sample: suggestive linkage on 17p11." *Am J Hum Genet*. 2003 May;72(5):1268-79. *Epub* 2003 Apr 08.

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Attention-deficit/hyperactivity disorder (ADHD [MIM 143465]) is a common, highly heritable neurobehavioral disorder of childhood onset, characterized by hyperactivity, impulsivity, and/or inattention. As part of an ongoing study of the genetic etiology of ADHD, we have performed a genomewide linkage scan in 204 nuclear families comprising 853 individuals and 270 affected sibling pairs (ASPs). Previously, we reported genomewide linkage analysis of a

"first wave" of these families composed of 126 ASPs. A follow-up investigation of one region on 16p yielded significant linkage in an extended sample. The current study extends the original sample of 126 ASPs to 270 ASPs and provides linkage analyses of the entire sample, using polymorphic microsatellite markers that define an approximately 10-cM map across the genome. Maximum LOD score (MLS) analysis identified suggestive linkage for 17p11 (MLS=2.98) and four nominal regions with MLS values >1.0, including 5p13, 6q14, 11q25, and 20q13. These data, taken together with the fine mapping on 16p13, suggest two regions as highly likely to harbor risk genes for ADHD: 16p13 and 17p11. Interestingly, both regions, as well as 5p13, have been highlighted in genomewide scans for autism.

1.3.6. Bakker, S.C., van der Meulen, E.M., Buitelaar, J.K., Sandkuijl, L.A., Pauls, D.L., Monsuur, A.J., van 't Slot, R., Minderaa, R.B., Gunning, W.B., Pearson, P.L., Sinke, R.J. "A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q." *Am J Hum Genet.* 2003 May;72(5):1251-60. *Epub* 2003 Apr 04.

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A genome scan was performed on 164 Dutch affected sib pairs (ASPs) with attention-deficit/hyperactivity disorder (ADHD). All subjects were white and of Dutch descent and were phenotyped according to criteria set out in the Diagnostic and Statistical Manual Of Mental Disorders, 4th edition. Initially, a narrow phenotype was defined, in which all the sib pairs met the full ADHD criteria (117 ASPs). In a broad phenotype, additional sib pairs were included, in which one child had an autistic-spectrum disorder but also met the full ADHD criteria (164 ASPs). A set of 402 polymorphic microsatellite markers with an average intermarker distance of 10 cM was genotyped and analyzed using the Mapmaker/sibs program. Regions with multipoint maximum likelihood scores (MLSs) >1.5 in both phenotypes were fine mapped with additional markers. This genome scan indicated several regions of interest, two of which showed suggestive evidence for linkage. The most promising chromosome region was located at 15q, with an MLS of 3.54 under the broad phenotype definition. This region was previously implicated in reading disability and autism. In addition, MLSs of 3.04 and 2.05 were found for chromosome regions 7p and 9q in the narrow phenotype. Except for a region on chromosome 5, no overlap was found with regions mentioned in the only other independent genome scan in ADHD reported to date.

1.3.7. Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I.C., Soderstrom, H., Giros, B., Leboyer, M., Gillberg, C., Bourgeron, T. "Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism." *Paris Autism Research International Sibpair Study. Nat Genet.* 2003 May;34(1):27-9.

Laboratoire de Genetique Humaine et Fonctions Cognitives, Universite Paris 7, Institut National de la Sante et la Recherche Medicale E0021, 75015 Paris, France.

Many studies have supported a genetic etiology for autism. Here we report mutations in two X-linked genes encoding neuroligins NLGN3 and NLGN4 in siblings with autism-spectrum disorders. These mutations affect cell-adhesion molecules localized at the synapse and suggest that a defect of synaptogenesis may predispose to autism.

1.3.8. Arbelle, S., Benjamin, J., Golin, M., Kremer, I., Belmaker, R.H., Ebstein, R.P. "Relation of shyness in grade school children to the genotype for the long form of the serotonin transporter promoter region polymorphism." *Am J Psychiatry.* 2003 Apr;160(4):671-6.

Unit for Child Psychiatry, Soroka Hospital, Beer Sheva, Israel.

OBJECTIVE: Studies have shown that genetic factors are significant in predisposing individuals to shyness and social phobia. Toward further elucidating the genetic structure of shyness, the authors examined four functional polymorphisms that make biological sense for contributing to the development of this phenotype: serotonin transporter promoter region 44 base pair insertion/deletion (5-HTTLPR), dopamine D(4) receptor exon III repeat (DRD4), catechol O-methyltransferase (COMT), and monoamine oxidase A promoter region repeat (MAO(A)). **METHOD:** The authors assessed shyness after recruitment of a nonclinical sample (N=118, unscreened second-grade children) using a composite scale derived from questionnaires administered to the children, parents, and teachers. DNA from buccal smears successfully obtained from 98 children was genotyped by polymerase chain reaction methods for the 5-HTTLPR, DRD4, COMT, and MAO(A) polymorphisms. **RESULTS:** Significant correlations were observed for parents', teachers', and children's ratings of shyness, and Cronbach's alpha reliability was high for all three scales. A significant association was observed between the long 5-HTTLPR polymorphism and shyness, both by the functional classification of Lesch as well as by consideration of all three genotypes. No significant association was observed for the DRD4, COMT, or MAO (A) polymorphisms. **CONCLUSIONS:** This study provisionally identifies a common genetic polymorphism, 5-HTTLPR, that mostly (effect size=7%) contributed to greater shyness scores in a nonclinical group of second-grade students. These first findings may be relevant to previous reports that have shown an association between the 5-HTTLPR long form and obsessive-compulsive disorder and autism.

1.3.9. Keller, K., Williams, C., Wharton, P., Paulk, M., Bent-Williams, A., Gray, B., Ward, A., Stalker, H., Wallace, M., Carter, R., Zori, R. "Routine cytogenetic and FISH studies for 17p11/15q11 duplications and subtelomeric rearrangement studies in children with autism spectrum disorders." *Am J Med Genet.* 2003 Mar 1;117A(2):105-11.

Raymond C Philips Unit, Division of Genetics, Department of Pediatrics, University of Florida, Gainesville, Florida 32610-0296, USA.

To assess the frequency of cytogenetic abnormalities in children with autism spectrum disorders (ASDs), routine G-banded cytogenetic analyses and FISH studies to rule out

15q11.2 and 17p11.2 duplications were performed on 49 children with ASDs. Blood samples were further studied using a complete set of subtelomeric FISH probes. Routine chromosome study showed that one child had a small duplication of chromosome 5: 46,XY,dup(5)(p?14.2p?15.1). Another child had an interstitial duplication of the Prader-Willi and Angelman syndrome critical region of chromosome 15, detected by FISH analysis. The detection of these two cases underscores the importance of obtaining routine chromosome and 15q11-q13 FISH analyses in children with ASDs. No instance of 17p11.2 duplication was observed. Subtelomeric analysis did not reveal abnormalities in any of the subjects. Copyright 2003 Wiley-Liss, Inc.

1.3.10. Shao, Y., Cuccaro, M.L., Hauser, E.R., Raiford, K.L., Menold, M.M., Wolpert, C.M., Ravan, S.A., Elston, L., Decena, K., Dornelly, S.L., Abramson, R.K., Wright, H.H., DeLong, G.R., Gilbert, J.R., Pericak-Vance, M.A. "Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes." *Am J Hum Genet.* 2003 Mar;72(3):539-48. Epub 2003 Feb 03.

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Autistic disorder (AutD) is a complex genetic disease. Available evidence suggests that several genes contribute to the underlying genetic risk for the development of AutD. However, both etiologic heterogeneity and genetic heterogeneity confound the discovery of AutD-susceptibility genes. Chromosome 15q11-q13 has been identified as a strong candidate region on the basis of both the frequent occurrence of chromosomal abnormalities in that region and numerous suggestive linkage and association findings. Ordered-subset analysis (OSA) is a novel statistical method to identify a homogeneous subset of families that contribute to overall linkage at a given chromosomal location and thus to potentially help in the fine mapping and localization of the susceptibility gene within a chromosomal area. For the present analysis, a factor that represents insistence on sameness (IS)—derived from a principal-component factor analysis using data on 221 patients with AutD from the repetitive behaviors/stereotyped patterns domain in the Autism Diagnostic Interview-Revised—was used as a covariate in OSA. Analysis of families sharing high scores on the IS factor increased linkage evidence for the 15q11-q13 region, at the GABRB3 locus, from a LOD score of 1.45 to a LOD score of 4.71. These results narrow our region of interest on chromosome 15 to an area surrounding the gamma-aminobutyric acid-receptor subunit genes, in AutD, and support the hypothesis that the analysis of phenotypic homogeneous subtypes may be a powerful tool for the mapping of disease-susceptibility genes in complex traits.

1.3.11. Smith, M., Woodroffe, A., Smith, R., Holguin, S., Martinez, J., Filipek, P.A., Modahl, C., Moore, B., Bocian, M.E., Mays, L., Laulhere, T., Flodman, P., Spence M.A. "Molecular genetic delineation of a deletion of chromosome 13q12->q13 in a patient with autism and auditory processing deficits." *Cytogenet Genome Res.* 2002;98(4):233-9.

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In a sporadic case of autism and language deficit due to auditory processing defects, molecular genetic studies revealed that a chromosomal deletion occurred in the 13q12->q13 region. No chromosome abnormalities were detected in the parents. We determined that the deletion occurred on the paternally derived chromosome 13. There are two previous reports of chromosome 13 abnormalities in patients with autism. The deletion in the subject described in this paper maps between the two chromosome 13 linkage peaks described by Bradford et al. (2001) in studies of subjects with autism and language deficits. The 9-Mb region deleted in the patient described here contains at least four genes that are expressed in brain and that play a role in brain development. They are NBEA, MAB21L1, DCAMKL1 and MADH9. These genes therefore represent candidate genes for autism and specific language deficits.

1.3.12. Dawson, G., Webb, S., Schellenberg, G.D., Dager, S., Friedman, S., Aylward, E., Richards, T. "Defining the broader phenotype of autism: genetic, brain, and behavioral perspectives." *Dev Psychopathol* 2002 Summer;14(3):581-611. Publication Types: Review, Review, Academic.

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Achieving progress in understanding the cause, nature, and treatment of autism requires an integration of concepts, approaches, and empirical findings from genetic, cognitive neuroscience, animal, and clinical studies. The need for such integration has been a fundamental tenet of the discipline of developmental psychopathology from its inception. It is likely that the discovery of autism susceptibility genes will depend on the development of dimensional measures of broader phenotype autism traits. It is argued that knowledge of the cognitive neuroscience of social and language behavior will provide a useful framework for defining such measures. In this article, the current state of knowledge of the cognitive neuroscience of social and language impairments in autism is reviewed. Following from this, six candidate broader phenotype autism traits are proposed: (a) face processing, including structural encoding of facial features and face movements, such as eye gaze; (b) social affiliation or sensitivity to social reward, pertaining to the social motivational impairments found in autism; (c) motor imitation ability, particularly imitation of body actions; (d) memory, specifically those aspects of memory mediated by the medial temporal lobe-prefrontal circuits; (e) executive function, especially planning and flexibility; and (f) Language ability, particularly those aspects of language that overlap with specific language impairment, namely, phonological processing.

1.3.13. Hallmayer, J., Glasson, E.J., Bower, C., Petterson, B., Croen, L., Grether, J., Risch, N. "On the twin risk in autism." *Am J Hum Genet* 2002 Oct;71(4):941-6

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Autism is considered by many to be the most strongly genetically influenced multifactorial childhood psychiatric disorder. In the absence of any known gene or genes, the main support for this is derived from family and twin studies. Two recent studies (Greenberg et al. 2001; Betancur et al. 2002) suggested that the twinning process itself is an important risk factor in the development of autism. If true, this would have major consequences for the interpretation of twin studies. Both studies compared the number of affected twin pairs among affected sib pairs to expected values in two separate samples of multiplex families and reported a substantial and significant excess of twin pairs. Using data from our epidemiological study in Western Australia, we investigated the possibility of an increased rate of autism in twins. All children born between 1980 and 1995 with autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified (PDD-NOS) were ascertained. Of the 465 children with a diagnosis, 14 were twin births (rate 30.0/1,000) compared to 9,640 children of multiple births out of a total of 386,637 births in Western Australia between 1980 and 1995 (twin rate weighted to number of children with autism or PDD per year 26.3/1,000). These data clearly do not support twinning as a substantial risk factor in the etiology of autism. We demonstrate that the high proportion of twins found in affected-sib-pair studies can be adequately explained by the high ratio of concordance rates in monozygotic (MZ) twins versus siblings and the distribution of family size in the population studied. Our results are in agreement with those of two similar studies by Croen et al. (2002) in California and Hultman et al. (2002) in Sweden.

1.3.14. Lamb, J.A., Parr, J.R., Bailey, A.J., Monaco, A.P. "Autism: in search of susceptibility genes." *Neuromolecular Med* 2002;2(1):11-28. Publication Types: Review, Review, Academic.

Wellcome Trust Centre for Human Genetics, Headington, Oxford, UK.

Autism is a neurodevelopmental disorder of unknown etiology. There is convincing data for the involvement of genetic factors in the development of autism, and the absence of any consistent evidence for an environmental, neuroanatomical, or biochemical cause has led to an increasing number of genetic studies to determine the basis of this complex disorder. The results of recent genetic linkage and candidate gene studies are reviewed in relation to the challenge of clinical and genetic heterogeneity, and prospects for the future of genetic research in autism are considered.

1.3.15. Vincent, J.B., Petek, E., Thevarkunnel, S., Kolozsvari, D., Cheung, J., Patel, M., Scherer, S.W. "The RAY1/ST7 tumor-suppressor locus on chromosome 7q31 represents a complex multi-transcript system." *Genomics* 2002 Sep;80(3):283-94

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We recently identified a novel gene, RAY1 (FAM4A1), which spans a translocation breakpoint at 7q31 in a patient with autism. This gene has more recently been reported to be a suppressor of tumorigenicity, ST7, although controversy surrounds this observation because subsequent reports have failed to corroborate these findings. Our further analysis of this locus reveals that it is composed of a multigene system that includes two noncoding sense strand genes (ST7OT3 and ST7OT4) that overlap with many alternative forms of the coding RAY1/ST7 transcript, and two noncoding genes on the antisense strand (ST7OT1 and ST7OT2). RAY1/ST7 was determined to have at least three different 5' exons with alternative start codons, one of which seems to be used almost exclusively in the brain. We have also identified a third alternative 3' end of RAY1/ST7 that uses exons from ST7OT3. ST7OT3 spans from intron 10 to exon 14 of RAY1/ST7 and includes several exons. ST7OT4 has at least seven exons and is transcribed on the sense strand between RAY1/ST7 exon 1 and a tropomyosin-like sequence, TPM3L2. ST7OT1 overlaps with the RAY1/ST7 exon 1 and promoter. ST7OT2 spans from RAY1/ST7 intron 9 to intron 1, and has multiple isoforms. We screened the exons of RAY1/ST7 and ST7OT1-3 for sequence variants in 90 unrelated autism probands and identified several rare variants, including a Ile361Val substitution. Although these variants were not observed in a control population, it is unclear whether they contribute to the autistic phenotype. We postulate that the apparent noncoding genes at the RAY1/ST7 locus may be regulatory RNAs. The RAY1/ST7 may generate at least 18 possible isoforms, with many more arising if other sense-strand exons from ST7OT3 and ST7OT4 are used in a selective and possibly tissue-specific manner.

1.3.16. Stromland, K., Philipson, E., Andersson Gronlund, M. "Offspring of male and female parents with thalidomide embryopathy: birth defects and functional anomalies." *Teratology* 2002 Sep;66(3):115-21.

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BACKGROUND: The aim of the study was to evaluate congenital malformations and functional anomalies in the offspring of Swedish parents with thalidomide embryopathy (TE). **METHODS:** Sixty-four children (29 girls, 35 boys) with ages ranging from 0-18 years, born to 34 Swedish parents (14 women, 20 men) with TE, were studied. Data on malformations and dysfunction were collected from medical records at maternity and child healthcare units, delivery units, hospitals, outpatient clinics and schools. **RESULTS:** Five children had both a mother and father with TE, 23 had a mother suffering from TE, and in 36 children the father had TE. One girl had a major malformation consisting of pulmonary stenosis, and single cases of minor physical features and positional deformities were observed. One boy had autism. Four children were born preterm, all to a TE mother. One child died within 24 hr after birth. Seven spontaneous abortions were registered, five of them in TE mothers. The cesarian section rate was 39% among the TE

mothers, compared to 14% among the non-TE mothers. CONCLUSIONS: Malformations or functional anomalies similar to those typical for TE were not found in this group of children born to Swedish parents with TE. Cesarean sections were more frequently performed in TE mothers, partly because of pelvic and uterine malformations. Copyright 2002 Wiley-Liss, Inc.

1.3.17. Manning, J.T., Bundred, P.E., Flanagan, B.F. "The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene?" *Med Hypotheses* 2002 Sep;59(3):334-6.

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The androgen receptor gene (AR) contains a domain which includes a variable number of CAG sequences and alleles with low numbers of CAG repeats show high transactivation activity when complexed with testosterone. The ratio of 2nd and 4th digit length (2D:4D) is negatively correlated with phenotypic effects of testosterone. Low numbers of CAG repeats and low 2D:4D are both associated with high sperm numbers and protection against breast cancer. This suggests that CAG number and 2D:4D are correlated i.e. low CAG number and low 2D:4D indicate high activation of androgen-responsive genes. Findings from AR studies predict that low 2D:4D will be associated with prostate and hepatocellular cancer, urolithiasis, ADHD, ankylosing spondylitis, spontaneous abortion, and polycystic ovaries, while high 2D:4D will be associated with motor neuron diseases and endometrial cancer. Findings from 2D:4D studies predict that short CAG length will be common in autism and Asperger's syndrome, while high numbers of CAG repeats will be found in men who are prone to early myocardial infarction.

1.3.18. Auranen, M., Vanhala, R., Varilo, T., Ayers, K., Kempas, E., Ylisaukko-Oja, T., Sinsheimer, J.S., Peltonen, L., Jarvela, I. "A genome-wide screen for autism-spectrum disorders: evidence for a major susceptibility locus on chromosome 3q25-27." *Am J Hum Genet* 2002 Oct;71(4):777-90

Department of Molecular Medicine, National Public Health Institute, University of Helsinki, Finland.

To identify genetic loci for autism-spectrum disorders, we have performed a two-stage genome-wide scan in 38 Finnish families. The detailed clinical examination of all family members revealed infantile autism, but also Asperger syndrome (AS) and developmental dysphasia, in the same set of families. The most significant evidence for linkage was found on chromosome 3q25-27, with a maximum two-point LOD score of 4.31 ($Z(\max)(\text{dom})$) for D3S3037, using infantile autism and AS as an affection status. Six markers flanking over a 5-cM region on 3q gave $Z(\max \text{ dom}) > 3$, and a maximum parametric multipoint LOD score (MLS) of 4.81 was obtained in the vicinity of D3S3715 and D3S3037. Association, linkage disequilibrium, and haplotype analyses provided some evidence for shared ancestor alleles on this chromosomal region among affected individuals, especially in the regional subisolate. Additional potential susceptibility

loci with two-point LOD scores > 2 were observed on chromosomes 1q21-22 and 7q. The region on 1q21-22 overlaps with the previously reported candidate region for infantile autism and schizophrenia, whereas the region on chromosome 7q provided evidence for linkage 58 cM distally from the previously described autism susceptibility locus (AUTS1).

1.3.19. Krebs, M.O., Betancur, C., Leroy, S., Bourdel, M.C., Gillberg, C., Leboyer, M. "Absence of association between a polymorphic GGC repeat in the 5' untranslated region of the reelin gene and autism." *Paris Autism Research International Sibpair (PARIS) Study. Mol Psychiatry* 2002;7(7):801-4.

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Autism is a complex neurodevelopmental disorder with severe cognitive and communication disabilities, that has a strong genetic predisposition. Reelin, a protein involved in neuronal migration during development, is encoded by a gene located on 7q22, within the candidate region on 7q showing increased allele sharing in previous genome scans. A case/control and family-based association study recently reported a positive association between a trinucleotide repeat polymorphism (GGC) located in the 5' untranslated region (UTR) of the reelin gene and autism. We performed a transmission disequilibrium test (TDT) analysis of the 5'UTR polymorphism in 167 families including 218 affected subjects (117 trios and 50 affected sib pairs) and found no evidence of linkage/association. Our results do not support previous findings and suggest that this GGC polymorphism of the reelin gene is unlikely to be a major susceptibility factor in autism and/or genetic heterogeneity.

1.3.20. Persico, A.M., Pascucci, T., Puglisi-Allegra, S., Militerni, R., Bravaccio, C., Schneider, C., Melmed, R., Trillo, S., Montecchi, F., Palermo, M., Rabinowitz, D., Reichelt, K.L., Conciatori, M., Marino, R., Keller, F. "Serotonin transporter gene promoter variants do not explain the hyperserotonemia in autistic children." *Mol Psychiatry* 2002;7(7):795-800.

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Autism is a biologically-heterogeneous disease. Distinct subgroups of autistic patients may be marked by intermediate phenotypes, such as elevated serotonin (5-HT) blood levels, potentially associated with different underlying disease mechanisms. This could lead to inconsistent genetic association results, such as those of prior studies on serotonin transporter (5-HTT) gene promoter variants and autistic disorder. Contributions of 5-HTT gene promoter alleles to 5-HT blood levels were thus investigated in 134 autistic patients and 291 first-degree relatives. Mean 5-HT blood levels are 11% higher in autistic patients carrying the L/L genotype, compared to patients with the S/S or S/L genotype; this trend is not observed in first-degree relatives. The probability of

inheriting L or S alleles is significantly enhanced in patients with 5-HT blood levels above or below the mean, respectively ($P < 0.05$), but quantitative TDT analyses yield a non-significant trend ($P = 0.10$), as this polymorphism explains only 2.5% of the variance in 5-HT blood levels of autistic patients. In conclusion, 5-HTT gene promoter variants seemingly exert a small effect on 5-HT blood levels in autistic children, which largely does not account for hyperserotoninemia. Nonetheless, the inconsistent outcome of prior association studies could partly stem from a selection bias of hyper- or hypo-serotonergic probands.

1.3.21. Smalley, S.L., Kustanovich, V., Minassian, S.L., Stone, J.L., Ogdie, M.N., McGough, J.J., McCracken, J.T., MacPhie, I.L., Francks, C., Fisher, S.E., Cantor, R.M., Monaco, A.P., Nelson, S.F. **"Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism."** *Am J Hum Genet* 2002 Oct;71(4):959-63.

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Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder in childhood and likely represents an extreme of normal behavior. ADHD significantly impacts learning in school-age children and leads to impaired functioning throughout the life span. There is strong evidence for a genetic etiology of the disorder, although putative alleles, principally in dopamine-related pathways suggested by candidate-gene studies, have very small effect sizes. We use affected-sib-pair analysis in 203 families to localize the first major susceptibility locus for ADHD to a 12-cM region on chromosome 16p13 (maximum LOD score 4.2; $P = .000005$), building upon an earlier genomewide scan of this disorder. The region overlaps that highlighted in three genome scans for autism, a disorder in which inattention and hyperactivity are common, and physically maps to a 7-Mb region on 16p13. These findings suggest that variations in a gene on 16p13 may contribute to common deficits found in both ADHD and autism.

1.3.22. Harvey, M.T., Kennedy, C.H. **"Polysomnographic phenotypes in developmental disabilities."** *Int J Dev Neurosci* 2002 Jun-Aug;20(3-5):443-8. Publication Types: Review, Review, Tutorial.

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People with developmental disabilities express a number of unique behavioral patterns that have both phylogenetic and ontogenetic origins. Researchers have identified distinct behavioral phenotypes among developmental disabilities expressed as language development, cognitive profiles, adaptive behavior, and self-injury/aggression. In this article, we discuss evidence for the presence of polysomnographic phenotypes in developmental disabilities. Researchers using behavioral and/or electrophysiological measures have

identified differences in sleep architecture among people with autism, Down syndrome, and fragile X syndrome. In general, the greater the level of mental retardation, the less time spent in rapid eye movement sleep. The presence of autism or Down syndrome is associated with fewer and briefer bouts of rapid eye movement sleep, and total sleep time. Autism is also associated with greater levels of undifferentiated sleep. These findings for autism and Down syndrome contrast with fragile X syndrome whose sleep architecture anomalies appear to be a function of mental retardation level.

1.3.23. Fenster, S.D., Garner, C.C. **"Gene structure and genetic localization of the PCLO gene encoding the presynaptic active zone protein Piccolo."** *Int J Dev Neurosci* 2002 Jun-Aug;20(3-5):161-71.

Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294-0021, USA.

Piccolo belongs to a family of presynaptic cytoskeletal proteins likely to be involved in the assembly and function of presynaptic active zones as sites of neurotransmitter release. Given that abnormalities in the formation of synaptic junctions are thought to contribute to cognitive dysfunction during brain development, we have analyzed and compared the gene structure of the Piccolo gene, PCLO, from humans and mice and determined their chromosomal localization. A comparison of the deduced amino acid sequence of cDNA clones encoding Piccolo from human, mouse, rat and chicken reveals the presence of distinct homology domains. Only subsets of these are also present in the structurally related active zone protein Bassoon indicating that Piccolo and Bassoon perform related but distinct functions at active zones. Characterization of the PCLO gene reveals the presence of 25 coding exons spread over 380kb of genomic DNA. The human PCLO gene maps to 7q11.23-q21.3, a region of chromosome 7 implicated as a linkage site for autism and Williams Syndrome suggesting that alterations in the expression of Piccolo or the PCLO gene could contribute to developmental disabilities and mental retardation.

1.3.24. Yamagata, T., Aradhya, S., Mori, M., Inoue, K., Momoi, M.Y., Nelson, D.L. **"The human secretin gene: fine structure in 11p15.5 and sequence variation in patients with autism."** *Genomics* 2002 Aug;80(2):185-94.

Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, USA.

Secretin is a peptide hormone involved in digestion that has been studied as a potential therapeutic agent in patients with autism. We characterized the human secretin locus to determine whether mutations in this gene might play a role in a fraction of autism patients. While the secretin gene (SCT) was not found to be mutated in the majority of autistic patients, rare heterozygous sequence variants were identified in three patients. We also investigated length variation in a variable number of tandem repeats (VNTR) immediately upstream of SCT and found no significant differences in length between patients with autism and normal controls. SCT is located on 11p15.5, adjacent to DRD4 and HRAS. This region

has been reported to be associated with both autism and attention deficit hyperactivity disorder (ADHD). Although imprinting is a characteristic of some genes in the vicinity, we could find no evidence for methylation of SCT in lymphoblast cells from patients or control individuals.

1.3.25. Sultana, R., Yu, C.E., Yu, J., Munson, J., Chen, D., Hua, W., Estes, A., Cortes, F., de la Barra, F., Yu, D., Haider, S.T., Trask, B.J., Green, E.D., Raskind, W.H., Distech, C.M., Wijsman, E., Dawson, G., Storm, D.R., Schellenberg, G.D., Villacres, E.C. "Identification of a novel gene on chromosome 7q11.2 interrupted by a translocation breakpoint in a pair of autistic twins." *Genomics* 2002 Aug;80(2):129-34.

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We report here the identification and characterization of a novel gene (AUTS2) that spans the 7q11.2 breakpoint in a monozygotic twin pair concordant for autism and a t(7;20) (q11.2;p11.2) translocation. AUTS2 is 1.2 Mb and has 19 exons. The predicted protein is 1295 amino acids and does not correspond to any known protein. DNA sequence analysis of autism subjects and controls revealed 22 biallelic polymorphic sites. For all sites, both alleles were observed in both cases and controls. Thus no autism-specific mutation was observed. Association analysis with two exonic polymorphic sites and linkage analysis of four dinucleotide repeat markers, two within and two flanking AUTS2, was negative. Thus, although it is unlikely that AUTS2 is an autism susceptibility gene for idiopathic autism, it may be the gene responsible for the disorder in the twins studied here.

1.3.26. Stromme, P., Mangelsdorf, M.E., Scheffer, I.E., Gecz, J. "Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in Aristaless related homeobox gene, ARX." *Brain Dev* 2002 Aug;24(5):266-8.

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Clinical data from 50 mentally retarded (MR) males in nine X-linked MR families, syndromic and non-specific, with mutations (duplication, expansion, missense, and deletion mutations) in the Aristaless related homeobox gene, ARX, were analysed. Seizures were observed with all mutations and occurred in 29 patients, including one family with a novel myoclonic epilepsy syndrome associated with the missense mutation. Seventeen patients had infantile spasms. Other phenotypes included mild to moderate MR alone, or with combinations of dystonia, ataxia or autism. These data suggest that mutations in the ARX gene are important causes of MR, often associated with diverse neurological manifestations. Copyright 2002 Elsevier Science B.V.

1.3.27. Wassink, T.H., Piven, J., Vieland, V.J., Pietila, J., Goedken, R.J., Folstein, S.E., Sheffield, V.C. "Evaluation of FOXP2 as an autism susceptibility gene." *Am J Med Genet* 2002 Jul 8;114(5):566-9.

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A mutation in the gene FOXP2 was recently identified as being responsible for a complicated speech and language phenotype in a single large extended pedigree. This gene is of interest to autism because it lies in one of the most consistently linked autism chromosomal regions of interest. We therefore tested this gene for its involvement in autism in a large sample of autism families. We completely sequenced the exon containing the mutation, screened the remaining coding sequence using SSCP technology, and identified and genotyped two novel intronic tetranucleotide repeat polymorphisms that were then analyzed for evidence of linkage and linkage disequilibrium (LD). We identified two families in which heterozygous deletions of a small number of glutamines in a long polyglutamine stretch were found in one parent and the autistic probands; no other non-conservative coding sequence changes were identified. Linkage and LD analyses were performed in 75 affected sibling pair families and in two subgroups of this sample defined by the presence/absence of severe language impairment. One allele appeared to have an opposite pattern of transmission in the language based subgroups, but otherwise the linkage and LD analyses were negative. We conclude that FOXP2 is unlikely to contribute significantly to autism susceptibility. Copyright 2002 Wiley-Liss, Inc.

1.3.28. Jones, M.B., Szatmari, P. "A risk-factor model of epistatic interaction, focusing on autism." *Am J Med Genet* 2002 Jul 8;114(5):558-6.

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Research to date on the genetics of autism has not uncovered a major susceptibility locus and indications are that a number of genes, perhaps as many as 15-20, may play detectable but minor roles in the etiology of the condition. To cope with this situation, a risk-factor model based on standard epidemiologic designs is proposed. The model supposes that adding a factor to a fixed set of existing factors always increases the total risk. Thus, according to the model genetic contributions cumulate but are not necessarily additive. A threshold, hence, epistasis is required. The model is applied to several conditions in which the risk of autism is elevated, some genetic (fragile X, tuberous sclerosis) and some exogenous (rubella and thalidomide embryopathies). Male gender is discussed as a risk factor. This approach is contrasted primarily with Gillberg and Coleman's view of autism as "a syndrome or series of syndromes caused by many different separate individual diseases." The principal point of difference is whether the effects of different causes cumulate or do not cumulate. In the present approach they do, in Gillberg and Coleman's they do not. Copyright 2002 Wiley-Liss, Inc.

1.3.29. Hammer, S., Dorrani, N., Dragich, J., Kudo, S., Schanen, C. "The phenotypic consequences of MECP2 mutations extend beyond Rett syndrome." *Ment Retard Dev Disabil Res Rev* 2002;8(2):94-8. Publication Types: Review, Review, Tutorial.

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Although MECP2 was initially identified as the causative gene in classic Rett syndrome (RTT), the gene has now been implicated in several phenotypes that extend well beyond the clinically defined disorder. MECP2 mutations have been found in people with various disorders, including neonatal onset encephalopathy, X-linked recessive mental retardation (MRX), classic and atypical RTT, autism, and Angelman syndrome, as well as mildly affected females and normal carrier females. To make matters more complex, in approximately 20% of classic sporadic RTT cases and more than 50% of affected sister pairs, no mutation in MECP2 has been found. X-chromosome inactivation patterns can clearly affect the phenotypic expression in females, while the effect of the type and position of the mutation is more apparent in the broader phenotype than in RTT. Both males and females are at risk, although an excess of paternally derived mutations are found in most cases of classic RTT. Thus, because of the range of disparate phenotypes, the gene may account for a relatively large portion of mental retardation in the population. Copyright 2002 Wiley-Liss, Inc.

1.3.30. Herzing, L.B., Cook, F.H. Jr, Ledbetter, D.H. "Allele-specific expression analysis by RNA-FISH demonstrates preferential maternal expression of UBE3A and imprint maintenance within 15q11- q13 duplications." *Hum Mol Genet* 2002 Jul 15;11(15):1707-18.

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15q11- q13 contains many imprinted genes, and undergoes duplicon-mediated rearrangements, including deletions, duplications and triplications, and generation of marker chromosomes. Abnormal phenotypes, including language delays and autism spectrum disorders, are primarily observed with maternal 15q11- q13 duplication. To determine possible epigenetic effects on expression within duplicated 15q11- q13 regions, we utilized RNA-FISH to directly observe gene expression. RNA-FISH, unlike RT-PCR, is polymorphism-independent, and it also detects relative levels of expression at each allele. Unamplified, gene-specific RNA signals were detected using cDNA probes. Subsequent DNA-FISH confirmed RNA signals and assigned parental origin by colocalization of genomic probes. SNRPN and NDN expression was detected primarily from paternal alleles. Control Dystrobrevin transcripts were detected equally from both alleles; however, maternal-UBE3A signals were consistently larger than paternal signals in normal fibroblasts and in neural-precursor cells. Larger UBE3A signals were also observed on one or both maternal alleles in a cell line carrying a maternal interstitial duplication, on both alleles of a maternally derived marker(15) chromosome, and occasionally on a paternal allele in a cell line carrying a paternal interstitial duplication. Expression of NDNL2, just distal to the duplicated region, was not markedly altered but paralleled changes in UBE3A expression. Excess total maternal-UBE3A RNA was confirmed by Northern blot analysis of cell lines

carrying 15q11- q13 duplications or triplications. These results demonstrate that: (1) UBE3A is imprinted in fibroblasts, lymphoblasts and neural-precursor cells; (2) allelic imprint status is maintained in the majority of cells upon duplication both in cis and in trans; and (3) alleles on specific types of duplications may exhibit an increase in expression levels/loss of expression constraints.

1.3.31. Borg, I., Squire, M., Menzel, C., Stout, K., Morgan, D., Willatt, L., O'Brien, P.C., Ferguson-Smith, M.A., Ropers, H.H., Tommerup, N., Kalscheuer, V.M., Sargan, D.R. "A cryptic deletion of 2q35 including part of the PAX3 gene detected by breakpoint mapping in a child with autism and a de novo 2;8 translocation." *J Med Genet* 2002 Jun;39(6):391-9.

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We report a de novo, apparently balanced (2;8)(q35;q21.2) translocation in a boy with developmental delay and autism. Cross species (colour) paint (Rx) and SKY FISH, forward and reverse chromosome painting, and FISH with subtelomeric probes were used to examine the patient's karyotype, but further rearrangements were not detected. FISH with region specific clones mapping near 2q35 and 8q21.2 breakpoints and STS mapping performed on the isolated derivative chromosomes were used to refine the location of the breakpoints further. A cryptic deletion of between 4.23 and 4.41 Mb in extent and involving at least 13 complete genes or transcription units was found at the breakpoint on 2q35. The deletion includes the promoter and 5' untranslated region of the paired box 3 (PAX3) gene. The child has very mild dystopia canthorum which may be associated with the PAX3 haploinsufficiency. The 8q21.2 breakpoint is within MMP16 which encodes matrix metalloproteinase 16. We postulate that the cryptic deletion and rearrangement are responsible for the patient's phenotype and that a gene (or genes) responsible for autism lies at 2q35 or 8q21.2. The results present a step towards identifying genes predisposing to autism.

1.3.32. Silva, A.E., Vayego-Lourenco, S.A., Fett-Conte, A.C., Goloni-Bertollo, E.M., Varella-Garcia, M. "Tetrasomy 15q11-q13 identified by fluorescence in situ hybridization in a patient with autistic disorder." *Arq Neuropsiquiatr* 2002 Jun;60(2-A):290-4.

Departamento de Biologia, IBILCE, State University of Sao Paulo, Sao Jose do Rio Preto, SP, Brasil.

We report a female child with tetrasomy of the 15q11-q13 chromosomal region, and autistic disorder associated with mental retardation, developmental problems and behavioral disorders. Combining classical and molecular cytogenetic approaches by fluorescence in situ hybridization technique, the karyotype was demonstrated as 47,XX,+mar.ish der(15)(D15Z1+,D15S11+,GABRB3+,PML-). Duplication of the 15q proximal segment represents the most consistent chromosomal abnormality reported in association with autism. The contribution of the GABA receptor subunit genes, and other genes mapped to this region, to the clinical symptoms of the disease is discussed.

1.3.33. Yu, C.E., Dawson, G., Munson, J., D'Souza, I., Osterling, J., Estes, A., Leutenegger, A.L., Flodman, P., Smith, M., Raskind, W.H., Spence, M.A., McMahon, W., Wijsman, F.M., Schellenberg, G.D. "Presence of large deletions in kindreds with autism." *Am J Hum Genet* 2002 Jul;71(1):100-15.

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Autism is caused, in part, by inheritance of multiple interacting susceptibility alleles. To identify these inherited factors, linkage analysis of multiplex families is being performed on a sample of 105 families with two or more affected sibs. Segregation patterns of short tandem repeat polymorphic markers from four chromosomes revealed null alleles at four marker sites in 12 families that were the result of deletions ranging in size from 5 to >260 kb. In one family, a deletion at marker D7S630 was complex, with two segments deleted (37 kb and 18 kb) and two retained (2,836 bp and 38 bp). Three families had deletions at D7S517, with each family having a different deletion (96 kb, 183 kb, and >69 kb). Another three families had deletions at D8S264, again with each family having a different deletion, ranging in size from <5.9 kb to >260 kb. At a fourth marker, D8S272, a 192-kb deletion was found in five families. Unrelated subjects and additional families without autism were screened for deletions at these four sites. Families screened included 40 families from Centre d'Etude du Polymorphisme Humaine and 28 families affected with learning disabilities. Unrelated samples were 299 elderly control subjects, 121 younger control subjects, and 248 subjects with Alzheimer disease. The deletion allele at D8S272 was found in all populations screened. For the other three sites, no additional deletions were identified in any of the groups without autism. Thus, these deletions appear to be specific to autism kindreds and are potential autism-susceptibility alleles. An alternative hypothesis is that autism-susceptibility alleles elsewhere cause the deletions detected here, possibly by inducing errors during meiosis.

1.3.34. Cowan, W.M., Kopnisky, K.L., Hyman, S.E. "The human genome project and its impact on psychiatry." *Annu Rev Neurosci* 2002;25:1-50. Publication Types: Review, Review, Academic.

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There has been substantial evidence for more than three decades that the major psychiatric illnesses such as schizophrenia, bipolar disorder, autism, and alcoholism have a strong genetic basis. During the past 15 years considerable effort has been expended in trying to establish the genetic loci associated with susceptibility to these and other mental disorders using principally linkage analysis. Despite this, only a handful of specific genes have been identified, and it is now generally recognized that further advances along these lines will require the analysis of literally hundreds of affected individuals and their families. Fortunately, the emergence in the past three years of a number of new approaches and more effective tools has given new hope to those engaged in the

search for the underlying genetic and environmental factors involved in causing these illnesses, which collectively are among the most serious in all societies. Chief among these new tools is the availability of the entire human genome sequence and the prospect that within the next several years the entire complement of human genes will be known and the functions of most of their protein products elucidated. In the meantime the search for susceptibility loci is being facilitated by the availability of single nucleotide polymorphisms (SNPs) and by the beginning of haplotype mapping, which tracks the distribution of clusters of SNPs that segregate as a group. Together with high throughput DNA sequencing, microarrays for whole genome scanning, advances in proteomics, and the development of more sophisticated computer programs for analyzing sequence and association data, these advances hold promise of greatly accelerating the search for the genetic basis of most mental illnesses while, at the same time, providing molecular targets for the development of new and more effective therapies.

1.3.35. Gousse V, Plumet MH, Chabane N, Mouren-Simeoni MC, Ferradian N, Leboyer M. "Fringe phenotypes in autism: a review of clinical, biochemical and cognitive studies." *Eur Psychiatry* 2002 May;17(3):120-8. Publication Types: Review, Review, Tutorial.

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Progress in identifying the genetic vulnerability factors in autism requires correct identification of the inherited phenotype(s). This can be achieved not only by the accurate description of the affected subject but also by the identification of vulnerability traits in non-affected relatives of autistic probands. This review will focus on this last strategy and principally on clinical, biochemical and cognitive traits.

1.3.36. Bartlett, C.W., Flax, J.F., Logue, M.W., Vieland, V.J., Bassett, A.S., Tallal, P., Brzustowicz, L.M. "A major susceptibility locus for specific language impairment is located on 13q21." *Am J Hum Genet* 2002 Jul;71(1):45-55.

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Children who fail to develop language normally-in the absence of explanatory factors such as neurological disorders, hearing impairment, or lack of adequate opportunity-are clinically described as having specific language impairment (SLI). SLI has a prevalence of approximately 7% in children entering school and is associated with later difficulties in learning to read. Research indicates that genetic factors are important in the etiology of SLI. Studies have consistently demonstrated that SLI aggregates in families. Increased monozygotic versus dizygotic twin concordance rates indicate that heredity, not just shared environment, is the cause of the familial clustering. We have collected five pedigrees of Celtic ancestry that segregate SLI, and we have conducted genomewide categorical linkage analysis, using model-based LOD score

techniques. Analysis was conducted under both dominant and recessive models by use of three phenotypic classifications: clinical diagnosis, language impairment (spoken language quotient <85) and reading discrepancy (nonverbal IQ minus non-word reading >15). Chromosome 13 yielded a maximum multipoint LOD score of 3.92 under the recessive reading discrepancy model. Simulation to correct for multiple models and multiple phenotypes indicated that the genomewide empirical P value is <.01. As an alternative measure, we also computed the posterior probability of linkage (PPL), obtaining a PPL of 53% in the same region. One other genomic region yielded suggestive results on chromosome 2 (multipoint I.OD score 2.86, genomic P value <.06 under the recessive language impairment model). Our findings underscore the utility of traditional I.OD-score-based methods in finding genes for complex diseases, specifically, SLI.

1.3.37. Klin, A., Jones, W., Schultz, R., Volkmar, F., Cohen, D. "Defining and quantifying the social phenotype in autism." *Am J Psychiatry* 2002 Jun;159(6):895-908. Publication Types: Review Review, Tutorial.

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OBJECTIVE: Genetic and neurofunctional research in autism has highlighted the need for improved characterization of the core social disorder defining the broad spectrum of syndrome manifestations. **METHOD:** This article reviews the advantages and limitations of current methods for the refinement and quantification of this highly heterogeneous social phenotype. **RESULTS:** The study of social visual pursuit by use of eye-tracking technology is offered as a paradigm for novel tools incorporating these requirements and as a research effort that builds on the emerging synergy of different branches of social neuroscience. **CONCLUSIONS:** Advances in the area will require increased consideration of processes underlying experimental results and a closer approximation of experimental methods to the naturalistic demands inherent in real-life social situations.

1.3.38. Torres, A.R., Maciulis, A., Stubbs, E.G., Cutler, A., Odell, D. "The transmission disequilibrium test suggests that HLA-DR4 and DR13 are linked to autism spectrum disorder." *Hum Immunol* 2002 Apr;63(4):311-6.

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We have evaluated possible contributions of HLA-DRB1 alleles to autism spectrum disorder (ASD) in 103 families of Caucasian descent. The DR4 allele occurred more often in probands than controls (0.007), whereas the DR13,14 alleles occurred less often in probands than controls ($p = 0.003$). The transmission disequilibrium test (TDT) indicated that the ASD probands inherited the DR4 allele more frequently than expected ($p = 0.026$) from the fathers. The TDT also revealed that fewer DR13 alleles than expected were inherited from the mother by ASD probands ($p = 0.006$). We conclude that the TDT results suggest that DR4 and DR13 are linked to ASD.

Reasons for the parental inheritance of specific alleles are poorly understood but coincide with current genetic research noting possible parent-of-origin effects in autism.

1.3.39. Li, H., Yamagata, T., Mori, M., Momoi, M.Y. "Association of autism in two patients with hereditary multiple exostoses caused by novel deletion mutations of EXT1." *J Hum Genet* 2002;47(5):262-5.

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Two boys from separate families presented with hereditary multiple exostoses (EXT) and autism associated with mental retardation. Their fathers both expressed a clinical phenotype of hereditary multiple exostoses milder than those of the patients and without the associated mental disorder. The EXT1 and EXT2 genes from lymphocytes of the affected individuals were analyzed by using denaturing high-performance liquid chromatography and direct sequencing. A novel deletion mutation, 1742delTGT-G in exon 9 of EXT1, causing a frameshift was detected in one boy and his father. Another novel deletion mutation, 2093delTT in exon 11 of EXT1, causing transcription termination was detected in the other affected boy and his father. EXT1 is expressed in the brain, and both EXT1 and EXT2 proteins are associated with glycosyltransferase activities required for the biosynthesis of heparan sulfate, which also has activity in the brain. The coincidental association of mental disorders in the boys was not completely excluded. However, these results suggest the involvement of EXT1 in the development of mental disorders, including mental retardation and autism.

1.3.40. Ijichi, S., Ijichi, N. "Minor form of trigonocephaly is an autistic skull shape? A suggestion based on homeobox gene variants and MECP2 mutations." *Med Hypotheses* 2002 Apr;58(4):337-9.

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A possible role for Hoxa1 genotype in susceptibility to autism spectrum disorders was recently proposed. Furthermore, it has been demonstrated that Rett syndrome, which is categorized into pervasive developmental disorders the same as the autism spectrum disorders, is associated with mutations in MECP2 gene. These findings suggest that the genetic backgrounds of these behavioral conditions may involve genes which also have an important role in the development of skull, because Hoxa1 is a key gene for skull development as well as for brain development and one of the clinical characteristics of Rett syndrome is deceleration in head growth. Together with this evolving knowledge, a series of ethical arguments concerning the indication of surgical treatment in patients with minor forms of trigonocephaly with autistic behaviors and/or hyperactivity leads us to hypothesize the presence of an autism subtype which may frequently be accompanied by specific morphological skull characteristics (autistic skull shape). Copyright 2002 Elsevier Science Ltd. All rights reserved.

1.3.41. Marie, S., Race, V., Nassogne, M.C., Vincent, M.F., Van den Berghe, G. "Mutation of a nuclear respiratory factor 2 binding site in the 5' untranslated region of the ADSL gene in three patients with adenylosuccinate lyase deficiency." *Am J Hum Genet* 2002 Jul;71(1):14-21.

Laboratory of Physiological Chemistry, Christian de Duve Institute of Cellular Pathology, and Universite Catholique de Louvain, Brussels, Belgium.

Adenylosuccinate lyase (ADSL; also called "adenylosuccinase") catalyzes two steps in the synthesis of purine nucleotides: (1) the conversion of succinylaminoimidazolecarboxamide ribotide into aminoimidazolecarboxamide ribotide and (2) the conversion of adenylosuccinate into adenosine monophosphate. ADSL deficiency, a recessively inherited disorder, causes variable-but most often severe-mental retardation, frequently accompanied by epilepsy and/or autism. It is characterized by the accumulation, in body fluids, of succinylaminoimidazolecarboxamide riboside and succinyladenosine, the dephosphorylated derivatives of the two substrates of the enzyme. Analysis of the ADSL gene of three unrelated patients with ADSL deficiency, in whom one of the ADSL alleles displayed a normal coding sequence, revealed a -49T->C mutation in the 5' untranslated region of this allele. Measurements of the amount of mRNA transcribed from the latter allele showed that it was reduced to approximately 33% of that transcribed from the alleles mutated in their coding sequence. Further investigations showed that the -49T->C mutation provokes a reduction to 25% of wild-type control of promoter function, as evaluated by luciferase activity and mRNA level in transfection experiments. The mutation also affects the binding of nuclear respiratory factor 2 (NRF-2), a known activator of transcription, as assessed by gel-shift studies. Our findings indicate that a mutation of a regulatory region of the ADSL gene might be an unusually frequent cause of ADSL deficiency, and they suggest a role for NRF-2 in the gene regulation of the purine biosynthetic pathway.

1.3.42. Zwaigenbaum, L., Szatmari, P., Jones, M.B., Bryson, S.E., MacLean, J.E., Mahoney, W.J., Bartolucci, G., Tuff, L. "Pregnancy and birth complications in autism and liability to the broader autism phenotype." *J Am Acad Child Adolesc Psychiatry* 2002 May;41(5):572-9.

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OBJECTIVE: To understand better the relationship between pregnancy and birth complications and genetic factors in autism. **METHOD:** The sample included 78 children with an autism spectrum disorder and 88 unaffected siblings. A standardized interview was used to ask mothers about the pregnancy and birth of each child, and an overall index reflecting freedom from complications (termed "optimality") was determined. The presence of autism-like traits (termed the "broader autism phenotype") in second- and third-degree relatives was ascertained by reports from multiple informants. The pro- portion of relatives with the broader autism

phenotype, corrected for degree of relation, was used as an index of family loading. **RESULTS:** Children with autism spectrum disorders have lower optimality (higher rates of complications) than unaffected siblings. High family loading for the broader autism phenotype is associated with higher rates of complications in unaffected siblings. Family loading was not significantly associated with complications in affected siblings in this sample. Overall, these findings argue against complications being a direct cause of autism, as one would expect to find the most complications in sporadic cases (i.e., in children without a positive family history). **CONCLUSION:** Increased rates of birth and pregnancy complications are likely secondary to familial factors associated with autism.

1.3.43. Wimpory, D., Nicholas, B., Nash, S. "Social timing, clock genes and autism: a new hypothesis." *J Intellect Disabil Res* 2002 May;46(Pt 4):352-8. Publication Types: Review, Review, Tutorial.

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BACKGROUND: Timing and social timing deficits are fundamental in autism and may play a developmental role in its manifestation. Sleep problems are associated with this disorder, as is a reduction or loss of Purkinje cells associated with regions of the brain which co-ordinate fine motor movements. Genetic studies suggest that a number of genes of limited effect lead to autism and that the genes are epistatic. **CONCLUSIONS:** We suggest that anomalies in clock genes operating as timing genes in high frequency oscillator systems may underlie the timing deficits of autism. We outline how anomalies in methylation-related genes may also be implicated.

1.3.44. Lauritsen, M.B., Borglum, A.D., Betancur, C., Philippe, A., Kruse, T.A., Leboyer, M., Ewald, H. "Investigation of two variants in the DOPA decarboxylase gene in patients with autism." *Am J Med Genet* 2002 May 8;114(4):466-70.

Department of Psychiatric Demography, Institute for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Risskov, Denmark.

Though genetic risk factors are important for the development of autism, no specific risk alleles have yet been identified. DOPA decarboxylase (DDC) is involved in both the catecholaminergic and serotonergic pathways and may be considered a functional candidate gene for autism. The present study is the first to test if two new variants of possible functional significance in the DDC gene increase the susceptibility to autism. A total of 90 parent-offspring trios recruited in Denmark and France were investigated using the transmission disequilibrium test (TDT). We found no evidence of linkage disequilibrium between autism and either of the two polymorphisms. Nor did we find linkage disequilibrium between autism and haplotypes of the two variants using a multiallelic TDT. These findings suggest that the DDC gene is unlikely to play a major role in the development of autism in our data set. Copyright 2002 Wiley-Liss, Inc.

1.3.45. Schutz, C.K., Polley, D., Robinson, P.D., Chalifoux, M., Macciardi, F., White, B.N., Holden, J.J. "Autism and the X chromosome: no linkage to microsatellite loci detected using the affected sibling pair method." *Am J Med Genet* 2002 Apr 15;109(1):36-41.

Department of Biology, McMaster University, Hamilton, Ontario, Canada.

The etiology of autism spectrum disorders (ASDs) is poorly understood, although it is clear that genetic factors play a major role. ASDs appear to be a heterogeneous group of disorders, making genetic analysis difficult in the absence of etiologically definable subgroups. The excess of males in the affected population has led to suggestions that an X-linked locus could play a role in the causation of autism or a related pervasive developmental disorder. To examine this, we have investigated the genotypes of 31 families with two or more affected boys, at a series of 16 highly polymorphic loci distributed along the X chromosome with an average interlocus distance of 12 cM, in order to identify regions of significantly increased concordance among pairs of affected brothers. No locus tested showed a significant increase in concordance, supporting findings by others that there are no genes of major effect located on the X chromosome that contribute to increased susceptibility to ASD. Copyright 2002 Wiley-Liss, Inc.

1.3.46. Szatmari, P., Merette, C., Bryson, S.E., Thivierge, J., Roy, M.A., Cayer, M., Maziade, M. "Quantifying dimensions in autism: a factor-analytic study." *J Am Acad Child Adolesc Psychiatry* 2002 Apr;41(4):467-74.

Department of Psychiatry and Behavioral Neurosciences, McMaster University, Hamilton, Ontario, Canada.

OBJECTIVE: The objective of this study was to determine whether the phenotypic variation in autism and the related pervasive developmental disorders (PDDs) is a unitary construct or whether it is composed of distinct dimensions of autistic symptoms and measures of level of functioning. **METHOD:** One hundred twenty-nine children with autism and other forms of PDD from two samples with different inclusion criteria were assessed with the Vineland Adaptive Behavior Scales to measure level of functioning and the Autism Diagnostic Interview to measure severity of autistic behaviors. A factor analysis with varimax rotation was performed on each sample, separately and combined. **RESULTS:** Two factors emerged; one representing autistic symptoms and another representing level of functioning. The factor structure was remarkably similar and robust to variations in ascertainment and inclusion criteria between the samples. The validity of the distinction was supported by differences between males and females on the symptom factor, but not on the level of functioning factor. IQ was modestly correlated with level of functioning, but not with symptoms. **CONCLUSIONS:** The phenotypic variation seen in autism/PDD is composed of at least two different dimensions of autistic symptoms and level of functioning. The implications of this dimensional heterogeneity for research, classification, and clinical practice are discussed.

1.3.47. Fisher, S.E., Francks, C., McCracken, J.T., McGough, J.J., Marlow, A.J., MacPhie, I.L., Newbury, D.F., Crawford, I.R., Palmer, C.G., Woodward, J.A., Del'Homme, M., Cantwell, D.P., Nelson, S.F., Monaco, A.P., Smalley, S.L. "A genomewide scan for loci involved in attention-deficit/hyperactivity disorder." *Am J Hum Genet* 2002 May;70(5):1183-96.

Wellcome Trust Centre for Human Genetics, Oxford University, Oxford, United Kingdom.

Attention deficit/hyperactivity disorder (ADHD) is a common heritable disorder with a childhood onset. Molecular genetic studies of ADHD have previously focused on examining the roles of specific candidate genes, primarily those involved in dopaminergic pathways. We have performed the first systematic genomewide linkage scan for loci influencing ADHD in 126 affected sib pairs, using a approximately 10-cM grid of microsatellite markers. Allele-sharing linkage methods enabled us to exclude any loci with a $\lambda(s)$ of $>$ or $=3$ from 96% of the genome and those with a $\lambda(s)$ of $>$ or $=2.5$ from 91%, indicating that there is unlikely to be a major gene involved in ADHD susceptibility in our sample. Under a strict diagnostic scheme we could exclude all screened regions of the X chromosome for a locus-specific $\lambda(s)$ of $>/=2$ in brother-brother pairs, demonstrating that the excess of affected males with ADHD is probably not attributable to a major X-linked effect. Qualitative trait maximum LOD score analyses pointed to a number of chromosomal sites that may contain genetic risk factors of moderate effect. None exceeded genomewide significance thresholds, but LOD scores were >1.5 for regions on 5p12, 10q26, 12q23, and 16p13. Quantitative-trait analysis of ADHD symptom counts implicated a region on 12p13 (maximum LOD 2.6) that also yielded a LOD >1 when qualitative methods were used. A survey of regions containing 36 genes that have been proposed as candidates for ADHD indicated that 29 of these genes, including DRD4 and DAT1, could be excluded for a $\lambda(s)$ of 2. Only three of the candidates-DRD5, 5HTT, and CALCYON-coincided with sites of positive linkage identified by our screen. Two of the regions highlighted in the present study, 2q24 and 16p13, coincided with the top linkage peaks reported by a recent genome-scan study of autistic sib pairs.

1.3.48. Yirmiya, N., Pilowsky, T., Tidhar, S., Nemanov, L., Altmark, L., Libstein, R.P. "Family-based and population study of a functional promoter-region monoamine oxidase A polymorphism in autism: possible association with IQ." *Am J Med Genet* 2002 Apr 8;114(3):284-7.

Department of Psychology, Hebrew University of Jerusalem, Jerusalem, Israel.

Although the etiology of autism remains to be elucidated, genetic elements significantly contribute to this disorder, and genes on the X chromosome are of special interest because there is a 4:1 predominance of male probands in autism. In the current study, we therefore examined, using the robust transmission disequilibrium test (TDT), possible preferential transmission of variants of a functional monoamine oxidase A (MAO A) promoter region polymorphism for linkage to

autism. In the 49 families examined (33 families with one proband and 15 families with two affected siblings), we did not find preferential transmission of MAO A from 33 heterozygous mothers to affected child (TDT chi-square = 0.29, NS). Nor was any significant difference in MAO A allele frequency observed between 43 male autism subjects versus a group of 108 non-autism control subjects (chi-square = 1.23, $P = 0.27$, NS). However, a trend was observed for an association between IQ in the probands and the MAO A genotype that just attained significance ($F = 3.5$, $P = 0.046$, $N = 28$) in the small group of autism subjects recruited from families with two affected siblings. Copyright 2002 Wiley-Liss, Inc.

1.3.49. Veenstra-VanderWeele, J., Kim, S.J., Lord, C., Courchesne, R., Akshoomoff, N., Leventhal, B.I., Courchesne, E., Cook, E.H. Jr. "Transmission disequilibrium studies of the serotonin 5-HT_{2A} receptor gene (HTR2A) in autism." *Am J Med Genet* 2002 Apr 8;114(3):277-83.

Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry, University of Chicago, Chicago, Illinois 60637, USA.

Hyperserotonemia in autism is one of the longest-standing biochemical findings in a psychiatric disorder. This well-replicated finding and subsequent studies of platelet serotonin receptors in autism indicate that the serotonin 2A receptor gene (HTR2A) on chromosome 13q is a primary candidate gene in autism. Converging data from recent genome screens also implicates the genomic region containing HTR2A. Based on these lines of evidence, the transmission/disequilibrium test (TDT) was used to assess transmission disequilibrium between autism and haplotypes of three polymorphisms, including the promoter -1438 G/A single nucleotide polymorphism (SNP) in perfect linkage disequilibrium with the 102 T/C SNP in previous studies, a newly identified SNP in intron 1 near exon 2, and the SNP responsible for the His452Tyr amino acid change in exon 3. Because expression studies have shown HTR2A to be polymorphically imprinted in the brain, secondary analyses were split into maternal and paternal transmissions. No evidence was found for unequal transmission of haplotypes; however, power analysis reveals low power to detect a parent-of-origin effect in this sample size. Copyright 2002 Wiley-Liss, Inc.

1.3.50. Buxbaum, J.D., Silverman, J.M., Smith, C.J., Greenberg, D.A., Kilifarski, M., Reichert, J., Cook, E.H. Jr, Fang, Y., Song, C.Y., Vitale, R. "Association between a GABRB3 polymorphism and autism." *Mol Psychiatry* 2002;7(3):311-6

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Autistic disorder (OMIM 209850) is a disease with a significant genetic component of a complex nature.(1) Cytogenetic abnormalities in the Prader-Willi/Angelman syndrome critical region (15q11-13) have been described in several individuals with autism.(1) For this reason, markers

across this region have been screened for evidence of linkage and association, and a marker (155CA-2) in the gamma-aminobutyric acid type-A receptor beta3 subunit gene (GABRB3) has been associated in one study(2) but not others.(3-5) We completed an association analysis with 155CA-2 using the transmission disequilibrium test (TDT) in a set of 80 autism families (59 multiplex and 21 trios). We also used four additional markers (69CA, 155CA-1, 85CA, and A55CA-1) localized within 150 kb of 155CA-2. The use of multi-allelic TDT (MTDT) ($P < 0.002$), as well as the TDT ($P < 0.004$), demonstrated an association between autistic disorder and 155CA-2 in these families. Meiotic segregation distortion could be excluded as a possible cause for these results since no disequilibrium was observed in unaffected siblings. These findings support a role for genetic variants within the GABA receptor gene complex in 15q11-13 in autistic disorder.

1.3.51. Jamain, S., Betancur, C., Quach, H., Philippe, A., Fellous, M., Giros, B., Gillberg, C., Leboyer, M., Bourgeron, T. "Linkage and association of the glutamate receptor 6 gene with autism." *Paris Autism Research International Sibpair (PARIS) Study. Mol Psychiatry* 2002;7(3):302-10.

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A genome scan was previously performed and pointed to chromosome 6q21 as a candidate region for autism. This region contains the glutamate receptor 6 (GluR6 or GRIK2) gene, a functional candidate for the syndrome. Glutamate is the principal excitatory neurotransmitter in the brain and is directly involved in cognitive functions such as memory and learning. We used two different approaches, the affected sib-pair (ASP) method and the transmission disequilibrium test (TDT), to investigate the linkage and association between GluR6 and autism. The ASP method, conducted with additional markers on the 51 original families and in eight new sibling pairs, showed a significant excess of allele sharing, generating an elevated multipoint maximum LOD score (ASPEX MLS = 3.28). TDT analysis, performed in the ASP families and in an independent data set of 107 parent-offspring trios, indicated a significant maternal transmission disequilibrium (TDTall $P = 0.0004$). Furthermore, TDT analysis (with only one affected proband per family) showed significant association between GluR6 and autism (TDT association $P = 0.008$). In contrast to maternal transmission, paternal transmission of GluR6 alleles was as expected in the absence of linkage, suggesting a maternal effect such as imprinting. Mutation screening was performed in 33 affected individuals, revealing several nucleotide polymorphisms (SNPs), including one amino acid change (M867I) in a highly conserved domain of the intracytoplasmic C-terminal region of the protein. This change is found in 8% of the autistic subjects and in 4% of the control population and seems to be more maternally transmitted than expected to autistic males ($P = 0.007$). Taken together, these data suggest that GluR6 is in linkage disequilibrium with autism.

1.3.52. Bonora, E., Bacchelli, E., Levy, E.R., Blasi, F., Marlow, A., Monaco, A.P., Maestrini, E. "Mutation screening and imprinting analysis of four candidate genes for autism in the 7q32 region." *International Molecular Genetic Study of Autism Consortium (IMGSAC). Mol Psychiatry* 2002;7(3):289-301.

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Genetic studies indicate that chromosome 7q is likely to contain an autism susceptibility locus (AUTS1). We have followed a positional candidate gene approach to identify the relevant gene and report the analysis of four adjacent genes localised to a 800 kb region in 7q32 that contains an imprinted domain: PEG1/MES1, COPG2, CPA1 and CPA5-a previously uncharacterised member of the carboxypeptidase gene family. Screening these genes for DNA changes and association analysis using intragenic single nucleotide polymorphisms (SNPs) provided no evidence for an etiological role in IMGSAC families. We also searched for imprinting mutations potentially implicated in autism: analysis of both DNA methylation and replication timing indicated a normal imprinting regulation of the PEG1/COPG2 domain in blood lymphocytes of all patients tested. The analysis of these four genes strongly suggests that they do not play a major role in autism aetiology, and delineates our strategy to screen additional candidate genes in the AUTS1 locus.

1.3.53. Kim, S.J., Cox, N., Courchesne, R., Lord, C., Corsello, C., Akshoomoff, N., Guter, S., Leventhal, B.L., Courchesne, E., Cook, E.H. Jr. "Transmission disequilibrium mapping at the serotonin transporter gene (SLC6A4) region in autistic disorder." *Mol Psychiatry* 2002;7(3):278-88.

Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry MC3077, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA.

The serotonin transporter gene (SLC6A4, MIM 182138) is a candidate gene in autistic disorder based on neurochemical, neuroendocrine studies and the efficacy of potent serotonin transporter inhibitors in reducing ritualistic behaviors and related aggression. An insertion/deletion polymorphism (5-HTTLPR) in the promoter region and a variable number of tandem repeat polymorphism (VNTR) in the second intron, were previously identified and suggested to modulate transcription. Six previous family-based association studies of SLC6A4 in autistic disorder have been conducted, with four studies showing nominally significant transmission disequilibrium and two studies with no evidence of nominally significant transmission disequilibrium. In the present study, TDT was conducted in 81 new trios. A previous finding of transmission disequilibrium between a haplotype consisting of the 5-HTTLPR and intron 2 VNTR was replicated in this study, but not preferential transmission of 5-HTTLPR as an independent marker. Because of inconsistent transmission of 5-HTTLPR across studies, SLC6A4 and its flanking regions were sequenced in 10 probands, followed by typing of 20 single nucleotide polymorphisms (SNPs) and seven simple

sequence repeat (SSR) polymorphisms in 115 autism trios. When individual markers were analyzed by TDT, seven SNP markers and four SSR markers (six SNPs, 5-HTTLPR and the second intron VNTR from promoter 1A through intron 2 of SLC6A4, one SSR from intron 7 of SLC6A4, one SNP from the bleomycin hydrolase gene (BLMH, MIM 602403) and one SSR telomeric to BLMH) showed nominally significant evidence of transmission disequilibrium. Four markers showed stronger evidence of transmission disequilibrium (TDT(max) $P = 0.0005$) than 5-HTTLPR.

1.3.54. Duffy, K., Al-Saleem, T., Karbowniczek, M., Ewalt, D., Prowse, A.H., Henske, E.P. "Mutational analysis of the von hippel lindau gene in clear cell renal carcinomas from tuberous sclerosis complex patients." *Mod Pathol* 2002 Mar;15(3):205-10.

Medical Oncology Division, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, USA.

Tuberous sclerosis complex (TSC) is an autosomal-dominant disorder characterized by seizures, mental retardation, autism, and tumors of multiple organs. Renal disease in TSC includes angiomyolipomas, cysts, and renal cell carcinomas. It is known that somatic mutations in the von Hippel Lindau (VHL) tumor suppressor gene occur in most clear cell renal carcinomas. To determine whether TSC-associated clear cell carcinomas also contain VHL mutations, we analyzed six tumors for loss of heterozygosity in the VHL gene region of chromosome 3p and for mutations in the VHL gene. Four of the patients were women between the ages of 34 and 68 years, and two were males under the age of 21 years. The loss of heterozygosity analysis was performed using polymorphic microsatellite markers, and the mutational analysis was performed using direct sequencing. Chromosome 3p loss of heterozygosity was not detected, and no VHL mutations were identified. These findings suggest that mutations in the TSC1 and TSC2 genes lead to clear cell renal carcinogenesis via an alternate pathway not involving VHL mutations.

1.3.55. Fantes, J.A., Mewborn, S.K., Lese, C.M., Hedrick, J., Brown, R.L., Dyomin, V., Chaganti, R.S., Christian, S.L., Ledbetter, D.H. "Organisation of the pericentromeric region of chromosome 15: at least four partial gene copies are amplified in patients with a proximal duplication of 15q." *J Med Genet* 2002 Mar;39(3):170-7.

Department of Human Genetics, University of Chicago, Chicago, IL 60637, USA.

Clinical cytogenetic laboratories frequently identify an apparent duplication of proximal 15q that does not involve probes within the PWS/AS critical region and is not associated with any consistent phenotype. Previous mapping data placed several pseudogenes, NF1, IgH D/V, and GABRA5 in the pericentromeric region of proximal 15q. Recent studies have shown that these pseudogene sequences have increased copy numbers in subjects with apparent duplications of proximal 15q. To determine the extent of variation in a control population, we analysed NF1 and IgH D pseudogene copy number in interphase nuclei from 20 cytogenetically normal

subjects by FISH. Both loci are polymorphic in controls, ranging from 1-4 signals for NF1 and 1-3 signals for IgH D. Eight subjects with apparent duplications, examined by the same method, showed significantly increased NF1 copy number (5-10 signals). IgH D copy number was also increased in 6/8 of these patients (4-9 signals). We identified a fourth pseudogene, BCL8A, which maps to the pericentromeric region and is coamplified along with the NF1 sequences. Interphase FISH ordering experiments show that IgH D lies closest to the centromere, while BCL8A is the most distal locus in this pseudogene array; the total size of the amplicon is estimated at approximately 1 Mb. The duplicated chromosome was inherited from either sex parent, indicating no parent of origin effect, and no consistent phenotype was present. FISH analysis with one or more of these probes is therefore useful in discriminating polymorphic amplification of proximal pseudogene sequences from clinically significant duplications of 15q.

1.3.56. Pujana, M.A., Nadal, M., Guitart, M., Armengol L, Gratacos M, Estivill X. "Human chromosome 15q11-q14 regions of rearrangements contain clusters of LCR15 duplicons." *Lur J Hum Genet* 2002 Jan;10(1):26-35

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Six breakpoint regions for rearrangements of human chromosome 15q11-q14 have been described. These rearrangements involve deletions found in approximately 70% of Prader-Willi or Angelman's syndrome patients (PWS, AS), duplications detected in some cases of autism, triplications and inverted duplications. HERC2-containing (HEct domain and RCc1 domain protein 2) segmental duplications or duplicons are present at two of these breakpoints (BP2 and BP3) mainly associated with deletions. We show here that clusters containing several copies of the human chromosome 15 low-copy repeat (LCR15) duplicon are located at each of the six described 15q11-q14 BPs. In addition, our results suggest the existence of breakpoints for large 15q11-q13 deletions in a proximal duplicon-containing clone. The study reveals that HERC2-containing duplicons (estimated on 50-400 kb) and LCR15 duplicons (approximately 15 kb on 15q11-q14) share the golgin-like protein (GLP) genomic sequence. Through the analysis of a human BAC library and public databases we have identified 36 LCR15 related sequences in the human genome, most (27) mapping to chromosome 15q and being transcribed. LCR15 analysis in non-human primates and age-sequence divergences support a recent origin of this family of segmental duplications through human speciation.

1.3.57. Korvatska, E., Van de Water, J., Anders, T.F., Gershwin, M.E. "Genetic and immunologic considerations in autism." *Neurobiol Dis* 2002 Mar;9(2):107-25. Publication Types: Review, Review Literature.

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According to recent epidemiological surveys, autistic spectrum disorders have become recognized as common childhood psychopathologies. These life-lasting conditions demonstrate a strong genetic determinant consistent with a polygenic mode of inheritance for which several autism susceptibility regions have been identified. Parallel evidence of immune abnormalities in autistic patients argues for an implication of the immune system in pathogenesis. This review summarizes advances in the molecular genetics of autism, as well as recently emerging concerns addressing the disease incidence and triggering factors. The neurochemical and immunologic findings are analyzed in the context of a neuroimmune hypothesis for autism. Studies of disorders with established neuroimmune nature indicate multiple pathways of the pathogenesis; herein, we discuss evidence of similar phenomena in autism. (c)2002 Elsevier Science (USA).

1.3.58. Newbury, D.F., Bonora, E., Lamb, J.A., Fisher, S.E., Lai, C.S., Baird, G., Jannoun, L., Slonims, V., Stott, C.M., Merricks, M.J., Bolton, P.F., Bailey, A.J., Monaco, A.P. "FOXP2 is not a major susceptibility gene for autism or specific language impairment." *International Molecular Genetic Study of Autism Consortium. Am J Hum Genet* 2002 May;70(5):1318-27

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The FOXP2 gene, located on human 7q31 (at the SPCH1 locus), encodes a transcription factor containing a polyglutamine tract and a forkhead domain. FOXP2 is mutated in a severe monogenic form of speech and language impairment, segregating within a single large pedigree, and is also disrupted by a translocation in an isolated case. Several studies of autistic disorder have demonstrated linkage to a similar region of 7q (the AUTS1 locus), leading to the proposal that a single genetic factor on 7q31 contributes to both autism and language disorders. In the present study, we directly evaluate the impact of the FOXP2 gene with regard to both complex language impairments and autism, through use of association and mutation screening analyses. We conclude that coding-region variants in FOXP2 do not underlie the AUTS1 linkage and that the gene is unlikely to play a role in autism or more common forms of language impairment.

1.3.59. Shao, Y., Raiford, K.L., Wolpert, C.M., Cope, H.A., Ravan, S.A., Ashley-Koch, A.A., Abramson, R.K., Wright, H.H., DeLong, R.G., Gilbert, J.R., Cuccaro, M.L., Pericak-Vance, M.A. "Phenotypic homogeneity provides increased support for linkage on chromosome 2 in autistic disorder." *Am J Hum Genet* 2002 Apr;70(4):1058-61.

Center for Human Genetics, CARL Building, Duke University Medical Center, Durham, NC 27710, USA.

Autistic disorder (AutD) is a neurodevelopmental disorder characterized by significant disturbances in social, communicative, and behavioral functioning. A two-stage genomic screen analysis of 99 families with AutD revealed suggestive evidence for linkage to chromosome 2q (D2S116 nonparametric sib-pair LOD score [MLS] 1.12 at 198 cM). In

addition, analysis of linkage disequilibrium for D2S116 showed an allele-specific P value of <.01. Recently, linkage to the same region of 2q was reported in an independent genome screen. This evidence for linkage increased when analysis was restricted to the subset of patients with AutD who had delayed onset (>36 mo) of phrase speech (PSD). We similarly classified our data set of 82 sib pairs with AutD, identifying 45 families with AutD and PSD. Analysis of this PSD subset increased our support for linkage to 2q (MLS 2.86 and HLOD 2.12 for marker D2S116). These data support evidence for a gene on chromosome 2 contributing to risk of AutD, and they suggest that phenotypic homogeneity increases the power to find susceptibility genes for AutD.

1.3.60. Kim, S.J., Herzing, L.B., Veenstra-VanderWeele, J., Lord, C., Courchesne, R., Leventhal, B.L., Ledbetter, D.H., Courchesne, E., Cook, E.H. Jr. "Mutation screening and transmission disequilibrium study of ATP10C in autism." *Am J Med Genet* 2002 Mar 8;114(2):137-43.

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Autism is a complex genetic disorder. Chromosome 15 is of particular interest in this disorder, because of previous reports of individuals with autism with chromosomal abnormalities in the 15q11-q13 region. Transmission disequilibrium between polymorphisms in this region and autism has been also been reported in some, but not all studies. Recently, a novel maternally expressed gene, ATP10C, was characterized and mapped to the chromosome 15q11-q13 region, 200 kb distal to UBE3A. It encodes a putative aminophospholipid translocase likely to be involved in the asymmetric distribution of proteins in the cell membrane. Preferential maternal expression has been demonstrated in fibroblasts and brain. Because of its physical location and imprinting pattern, ATP10C was considered to be a candidate gene for chromosome 15-associated autism. In an effort to find the genes responsible for autism in this chromosomal region, 1.5 kb of the 5' flanking region, as well as the coding and splicing regions of ATP10C, were screened for sequence variants. Several polymorphic markers including five nonsynonymous SNPs were identified. To investigate transmission disequilibrium between ATP10C and autism, a family-based association study was conducted for 14 markers in 115 autism trios. No significant transmission disequilibrium was found, suggesting ATP10C is unlikely to contribute strongly to susceptibility to autism in these families. However, due to limited power to detect genes of modest effect, the possible functional role of the nonsynonymous SNPs and the functional implications of the SNPs identified from 5' flanking region and intron 2 splicing region may be evaluated in further studies. Copyright 2002 Wiley-Liss, Inc.

1.3.61. Spiker, D., Iotspeich, L.J., Dimiceli, S., Myers, R.M., Risch, N. "Behavioral phenotypic variation in autism multiplex families: evidence for a continuous severity gradient." *Am J Med Genet* 2002 Mar 8;114(2):129-36

Division of Child Psychiatry and Child Development, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA.

Recent genetic investigations of autism have studied multiplex families, typically including families with multiple siblings who meet criteria for a diagnosis of autism. However, little is known about the specific behavioral characteristics of siblings with autism in these multiplex families. We investigated the behavioral phenotypic variability and similarity of 351 siblings with autism in 171 multiplex families using cluster analysis and correlations. The results of cluster analyses showed that the individuals with autism could be characterized on a severity gradient: a continuum based on severity of symptoms and impairment as measured by Autism Diagnostic Interview-Revised (ADI-R) scores, verbal-nonverbal status, and nonverbal IQ scores. Clusters based on scores from the ADI-R for the autism diagnostic criteria of the DSM-IV and nonverbal IQ scores still represented a severity gradient when the effects of verbal-nonverbal status were removed. The severity gradient was shown to be heritable, with a sib correlation of 30% or a heritability of 60%. In summary, in a sample of 171 autism multiplex families, there was no evidence of discrete behaviorally defined subgroups of affected individuals or families characterized by distinct patterns of behavioral symptoms. Rather, the clusters could be characterized along a single, heritable, continuous severity dimension. Copyright 2002 Wiley-Liss, Inc.

1.3.62. Philippe, A., Guilloud-Bataille, M., Martinez, M., Gillberg, C., Rastam, M., Sponheim, E., Coleman, M., Zappella, M., Aschauer, H., Penet, C., Feingold, J., Brice, A., Leboyer, M. "Analysis of ten candidate genes in autism by association and linkage." *Paris Autism Research International Sibpair Study. Am J Med Genet* 2002 Mar 8;114(2):125-8.

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We studied the possible involvement of ten candidate genes in autism: proenkephalin, prodynorphin, and proprotein convertase subtilisin/kexin type 2 (opioid metabolism); tyrosine hydroxylase, dopamine receptors D2 and D5, monoamine oxidases A and B (monoaminergic system); brain-derived neurotrophic factor, and neural cell adhesion molecule (involved in neurodevelopment). Thirty-eight families with two affected siblings and one family with two affected half-siblings, recruited by the Paris Autism Research International Sibpair Study (PARIS), were tested using the transmission disequilibrium test and two-point affected sib-pair linkage analysis. We found no evidence for association or linkage with intragenic or linked markers. Our family sample has good power for detecting a linkage disequilibrium of 0.80. Thus, these genes are unlikely to play a major role in the families studied, but further studies in a much larger sample would be needed to highlight weaker genetic effects. Copyright 2002 Wiley-Liss, Inc.

1.3.63. Beyer, K.S., Klauck, S.M., Benner, A., Poustka, F., Poustka, A. "Association studies of the HOPA dodecamer duplication variant in different subtypes of autism." *Am J Med Genet* 2002 Jan 8;114(1):110-5.

Department of Molecular Genome Analysis, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

The HOPA gene in Xq13 is coding for a protein involved in a nuclear thyroid receptor complex. Previous studies suggested association of the dodecamer duplication in the OPA-repeat region in exon 43 (according to the genomic database sequence) with autism, mental retardation, and schizophrenia/hypothyroidism. We determined the frequency of this 12 bp duplication variant in a sample of 155 patients divided in different subtypes of autism, 278 parents of those patients, and 157 control individuals. The allele frequency of the duplication variant was not significantly different between autistic patients, their parents, and the control group. Therefore, it is unlikely that this 12 bp duplication variant of the HOPA gene has major relevance to the susceptibility to different subtypes of autism at least in this German patient sample. In addition, we identified a third variant with a 15 bp deletion in the OPA-repeat region, recently described by another group, in one autistic patient. This third allele was also present in the patient's nonautistic mother and sister, who are heterozygous for this variant, but could not be detected in any other individual genotyped in this study. Expression analysis revealed transcription of all three allelic variants in lymphoblastoid cell lines. Furthermore, we identified a new splice variant that utilizes an additional 9 bp of the 3' intron subsequent to exon 39. Both alternative transcripts are coexpressed in all fetal and adult tissues examined. Copyright 2001 Wiley-Liss, Inc.

1.3.64. McCoy, P.A., Shao, Y., Wolpert, C.M., Donnelly, S.L., Ashley-Koch, A., Abel, H.L., Ravan, S.A., Abramson, R.K., Wright, H.H., DeLong, G.R., Cuccaro, M.L., Gilbert, J.R., Pericak-Vance, M.A. "No association between the WNT2 gene and autistic disorder." *Am J Med Genet* 2002 Jan 8;114(1):106-9.

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Autistic disorder is a pervasive neurodevelopmental disorder characterized by deficits in language and social communication, as well as stereotyped patterns of behavior. Peak LOD scores from several genomic screening efforts indicate the presence of an autistic disorder susceptibility locus within the distal long arm of human chromosome 7 (7q31-q35). Wassink et al. [2001: *Am J Med Genet* 105:406-413] reported that WNT2, located at 7q31, influences genetic risk in autistic disorder. These findings were enhanced when examined in a subset of families with severe language impairment. WNT genes encode secreted growth factor-like proteins that participate in growth regulation, differentiation, and tumorigenesis. We tested for genetic association of two WNT2 variants in an independent data set of 135 singleton and 82 multiplex families. No significant association was found between autistic disorder and the WNT2 genotypes in either the overall data set or in the language-impaired subset of families. However, differences in allele frequencies of the 3' UTR single nucleotide polymorphism between the present population and that of Wassink et al. may account for the inability to detect association between WNT2 and autistic

disorder in the present data set. We also screened the two reported autistic disorder mutations previously detected by Wassink et al. We did not identify any activating mutation in the coding region of the WNT2 gene. Thus, we conclude that activating mutations of the WNT2 gene are not a major contributor to the development of autistic disorder in these data. Copyright 2001 Wiley-Liss, Inc.

1.3.65. Shao, Y., Wolpert, C.M., Raiford, K.L., Menold, M.M., Donnelly, S.L., Ravan, S.A., Bass, M.P., McClain, C., von Wendt, L., Vance, J.M., Abramson, R.H., Wright, H.H., Ashley-Koch, A., Gilbert, J.R., DeLong, R.G., Cuccaro, M.L., Pericak-Vance, M.A. "Genomic screen and follow-up analysis for autistic disorder." *Am J Med Genet* 2002 Jan 8;114(1):99-105.

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Autistic disorder (AutD) is a neurodevelopmental disorder characterized by significant impairment in social, communicative, and behavioral functioning. A genetic basis for AutD is well established with as many as 10 genes postulated to contribute to its underlying etiology. We have completed a genomic screen and follow-up analysis to identify potential AutD susceptibility loci. In stage one of the genome screen, 52 multiplex families (two or more AutD affected individuals/family) were genotyped with 352 genetic markers to yield an approximately 10 centimorgan (cM) grid, inclusive of the X chromosome. The selection criterion for follow-up of interesting regions was a maximum heterogeneity lod score (MLOD) or a maximum nonparametric sib pair lod score (MLS) of at least 1.0. Eight promising regions were identified on chromosomes 2, 3, 7, 15, 18, 19, and X. In the stage two follow-up study we analyzed an additional 47 multiplex families (total=99 families). Regions on chromosomes 2, 3, 7, 15, 19, and X remained interesting (MLOD \geq or =1.0) in stage two analysis. The peak lod score regions on chromosomes 2, 7, 15, 19, and X overlap previously reported peak linkage areas. The region on chromosome 3 is unique. Copyright 2001 Wiley-Liss, Inc.

1.3.66. Silverman, J.M., Smith, C.J., Schmeidler, J., Hollander, E., Lawlor, B.A., Fitzgerald, M., Buxbaum, J.D., Delaney, K., Galvin, P. "Symptom domains in autism and related conditions: evidence for familiarity." *Autism Genetic Research Exchange Consortium. Am J Med Genet* 2002 Jan 8;114(1):64-73.

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Heterogeneity in autism impairs efforts to localize and identify the genes underlying this disorder. As autism comprises severe but variable deficits and traits in three symptom domains (social interaction, communication, and repetitive behaviors) and shows variability in the presence and emergence of useful phrase speech, different genetic factors may be associated with each. The affected cases (n=457) in multiply affected sibships (n=212), including a proband

with autism and one or more siblings with either autism or marked deficits in autism symptom domains, were assessed using the Autism Diagnostic Interview, Revised. Symptom domain scores and language features were examined to determine their similarity within sibblingships. The variance within sibblingships was reduced for the repetitive behavior domain and for delays in and the presence of useful phrase speech. These features and the nonverbal communication subdomain provided evidence of familiarity when we considered only the diagnosis of autism to define multiply affected sibblingships (cases: n=289; sibblingships: n=136). In addition, the same familial features identified also appeared familial for those with autism-related conditions. Finally, the level of severity of almost all of the familial features varied within multiplex sibblingships independently. The features identified as familial replicate the combined set suggested in earlier, smaller studies. Furthermore, the familiarity of these features extend to related conditions of milder severity than autism and appear to be independent. Making distinctions among families by the severity of these features may be useful for identifying more genetically homogeneous subgroups in studies targeted at genes for specific autism-related symptom domains. Copyright 2001 Wiley-Liss, Inc.

1.3.67. Li, J., Tabor, H.K., Nguyen, L., Gleason, C., Lotspeich, L.J., Spiker, D., Risch, N., Myers, R.M. "Lack of association between HoxA1 and HoxB1 gene variants and autism in 110 multiplex families." *Am J Med Genet* 2002 Jan 8;114(1):24-30.

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A recent report suggested that the HoxA1 and/or HoxB1 genes play a role in susceptibility to autism. To determine whether these findings could be confirmed, we screened these genes for DNA polymorphisms by sequencing all exons in 24 individuals with autism. We identified the same sequence variants in the genes that appeared in this report, which include one single-base substitution variant in HoxA1 and a common haplotype in HoxB1. We performed an association study by applying the transmission disequilibrium test to detect possible association of these variants to autism in 110 multiplex families. Our results demonstrated no deviation from the null hypothesis of no association. We have also separately examined transmissions within individual mating types, for paternal versus maternal alleles, to affected versus unaffected children, and for transmission to affected boys versus girls. None of these subsets revealed significant deviation from the null expectation. Our interpretation of these findings is that it is unlikely that HoxA1 and HoxB1 play a significant role in the genetic predisposition to autism. Copyright 2001 Wiley-Liss, Inc.

1.3.68. Jamain, S., Quach, H., Quintana-Murci, L., Betancur, C., Philippe, A., Gillberg, C., Sponheim, E., Skjeldal, O.H., Fellous, M., Leboyer, M., Bourgeron, T. "Y chromosome haplogroups in autistic subjects." *Mol Psychiatry* 2002;7(2):217-9.

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The male to female ratio in autism is 4:1 in the global autistic population, but increases to 23:1 in autistic subjects without physical or brain abnormalities.(1) Despite this well-recognized gender difference, male predisposition to autistic disorder remains unexplained and the role of sex chromosomes is still debated. Numerical and structural abnormalities of the sex chromosomes are among the most frequently reported chromosomal disorders associated with autism. However, genome scans have failed to detect linkage on the X chromosome(2,3,4) and this approach cannot study the non-recombining region of the Y chromosome. In this study, we searched for a specific Y chromosome effect in autistic subjects. Using informative Y-polymorphic markers, the Y chromosome haplotypes of 111 autistic subjects from France, Sweden and Norway were defined and compared with relevant control populations. No significant difference in Y-haplotype distribution between the affected and control groups was observed. Although this study cannot exclude the presence of a Y susceptibility gene, our results are not suggestive of a Y chromosome effect in autism.

1.3.69. Wolff, D.J., Clifton, K., Karr, C., Charles, J. "Pilot assessment of the subtelomeric regions of children with autism: detection of a 2q deletion." *Genet Med* 2002 Jan-Feb;4(1):10-4.

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PURPOSE: Autism is a chronic neurodevelopmental disorder characterized by deficits in reciprocal social interaction, language and communication, and by the presence of stereotypical behaviors. The disorder is a complex genetic trait with no known predisposing genes. We report the results of a pilot project to screen for aberrations in the gene-rich subtelomeric chromosomal regions of a cohort of children with autism. METHODS: For our pilot project, we used a multiprobe system that includes probes for the subtelomeric regions of all human chromosomes. We assessed the subtelomeric regions of chromosomes from 10 children with a diagnosis of autism. RESULTS: The screen identified one child with an apparent deletion of the subtelomeric region of chromosome 2q; nine children and pooled control samples yielded normal results. The deletion in our patient was confirmed with two other subtelomeric probes and a targeted cytogenetic study revealed a subtle difference in appearance for one chromosome 2 homologue. CONCLUSION: There have been several reports of children with dysmorphic features, autistic behaviors, and 2q deletions detectable with standard cytogenetic techniques. It may be that the distal region of chromosome 2q harbors a gene or genes that may predispose to autism.

1.3.70. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E. "Minicolumnar pathology in autism." *Neurology* 2002 Feb 12;58(3):428-32.

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OBJECTIVE: To determine whether differences exist in the configuration of minicolumns between the brains of autistic and control patients. **BACKGROUND:** Autism is a severe and pervasive developmental disturbance of childhood characterized by disturbances in both social interactions and communication, as well as stereotyped patterns of interests, activities, and behaviors. Postmortem neuropathologic studies remain inconclusive. **METHODS:** The authors used a computerized imaging program to measure details of cell column morphologic features in area 9 of the prefrontal cortex and areas 21 and posterior 22 (Tpt) within the temporal lobe of nine brains of autistic patients and controls. **RESULTS:** The authors found significant differences between brains of autistic patients and controls in the number of minicolumns, in the horizontal spacing that separates cell columns, and in their internal structure, that is, relative dispersion of cells. Specifically, cell columns in brains of autistic patients were more numerous, smaller, and less compact in their cellular configuration with reduced neuropil space in the periphery. **CONCLUSIONS:** In autism, there are minicolumnar abnormalities in the frontal and temporal lobes of the brain.

1.3.71. Andres, C. "Molecular genetics and animal models in autistic disorder." *Brain Res Bull* 2002 Jan 1;57(1):109-19. Publication Types: Review, Review, Academic.

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Autistic disorder is a behavioural syndrome beginning before the age of 3 years and lasting over the whole lifetime. It is characterised by impaired communication, impaired social interactions, and repetitive interests and behaviour. The prevalence is about 7/10,000 taking a restrictive definition and more than 1/500 with a broader definition, including all the pervasive developmental disorders. The importance of genetic factors has been highlighted by epidemiological studies showing that autistic disorder is one of the most genetic neuropsychiatric diseases. The relative risk of first relatives is about 100-fold higher than the risk in the normal population and the concordance in monozygotic twin is about 60%. Different strategies have been applied on the track of susceptibility genes. The systematic search of linked loci led to contradictory results, in part due to the heterogeneity of the clinical definitions, to the differences in the DNA markers, and to the different methods of analysis used. An oversimplification of the inferred model is probably also cause of our disappointment. More work is necessary to give a clearer picture. One region emerges more frequently: the long arm of chromosome 7. Several candidate genes have been studied and some gave indications of association: the Reelin gene and the Wnt2 gene. Cytogenetical abnormalities are frequent at 15q11-13, the region of the Angelman and Prader-Willi syndrome. Imprinting plays an important role in this region, no candidate gene has been identified in autism. Biochemical abnormalities have been found in the serotonin system. Association and linkage studies gave no consistent

results with some serotonin receptors and in the transporter, although it seems interesting to go further in the biochemical characterisation of the serotonin transporter activity, particularly in platelets, easily accessible. Two monogenic diseases have been associated with autistic disorder: tuberous sclerosis and fragile X. A better knowledge of the pathophysiology of these disorders can help to understand autism. Different other candidate genes have been tested, positive results await replications in other samples. Animal models have been developed, generally by knocking out the different candidate genes. Behaviour studies have mainly focused on anxiety and learning paradigms. Another group of models results from surgical or toxic lesions of candidate regions in the brain, in general during development. The tools to analyse these animals are not yet standardised, and an important effort needs to be undertaken.

1.3.72. Niklasson, L., Rasmussen, P., Oskarsdottir, S., Gillberg, C. "Chromosome 22q11 deletion syndrome (CATCH 22): neuropsychiatric and neuropsychological aspects." *Dev Med Child Neurol* 2002 Jan;44(1):44-50.

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Twenty children and young adults (age range 5 to 33 years, 12 females and eight males) with genetically confirmed 22q11 deletion syndrome (CATCH 22: Cardiac anomaly, Anomalous face, Thymus hypoplasia/aplasia, Cleft palate, and Hypocalcaemia), recruited from a large ongoing study, were given comprehensive assessments with a view to determining the pattern of neuropsychiatric and neuropsychological deficits thought to be part of the syndrome in many cases. IQ ranged between 46 and 100 with a mean score of 70. Half the group had an IQ <70. In 13 individuals, attention-deficit-hyperactivity disorder (ADHD), mainly inattentive or combined type in most cases, and/or autism spectrum problems were diagnosed. Many participants, even among those who had an IQ within the normal range and had neither ADHD nor autistic spectrum problems, showed a characteristic and pronounced behavioural profile with low mental energy, initiation difficulties, deficits in sustained attention, and social interaction (often augmented by limited facial expression and communication and speech problems).

1.3.73. Betancur, C., Corbex, M., Spielow, C., Phillippe, A., Laplanche, J.L., Launay, J.M., Gillberg, C., Mouren - Simeoni, M.C., Hamon, M., Giros, B., Nosten- Bertrand, M., Leboyer, M. "Serotonin transporter gene polymorphisms and hyperserotonemia in autistic disorder." *Mol Psychiatry* 2002; 67-71.

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Previous studies have provided conflicting evidence regarding the association of the serotonin transporter (5-HTT) gene with autism. Two polymorphisms have been identified in the human 5-HTT gene, a VNTR in intron 2 and a functional deletion/insertion in the promoter region (5-HTTLPR) with short and long variants. Positive associations of the 5-HTTLPR

polymorphism with autism have been reported by two family-based studies, but one found preferential transmission of the short allele and the other of the long allele. Two subsequent studies failed to find evidence of transmission disequilibrium at the 5-HTTLPR locus. These conflicting results be due to heterogeneity of clinical samples with regard to serotonin (5-HT) blood levels, which have been found to be elevated in some autistic subjects. Thus, we examined the association of the 5-HTTLPR and VNTR polymorphisms of the 5-HTT gene with autism, and we investigated the relationship between 5-HTT variants and whole blood 5-HT. The transmission / disequilibrium test (TDT) revealed no linkage disequilibrium at either loci in a sample of 96 families comprising 43 trios and 53 sib pairs. Furthermore, no significant relationship between 5-HT blood levels and 5-HTT gene polymorphisms was found. Our results suggest that the 5-HTT gene is unlikely to play a major role as a susceptibility factor in autism.

1.3.74. Badner, J.A., Gershon, E.S. "Regional meta-analysis of published data supports linkage of autism with markers on chromosome 7." *Mol Psychiatry* 2002, 7(1) : 56-66. Publication Types: Meta-Analysis.

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Although the concept of meta-analysis of multiple linkage scans of a genetic trait is not new, it can be difficult to apply to published data given the lack of consistency in the presentation of linkage results. In complex inheritance common diseases, there are many instances where one or two studies meet genome-wide criteria for significant or suggestive linkage but several other studies do not show even nominally significant results with the same region. One possibility for resolving differences between study results would be to combine an available result parameter of several studies. We describe here a method of regional meta-analysis, the multiple-scan probability (MSP), which can be used on published results. It combines the reported P-values of individual studies, after correcting each value for the size of the region containing a minimum P-value. Analysis of the power of MSP and of its type I error rates are presented. The type I error rate is at least as low as that for a single genome scan and thus genome-wide significance criteria may be applied. We also demonstrate appropriate criteria for that study is used to define a region of interest and then included, and when that study is used to define a region of interest and then excluded. In our simulations, meta-analysis to the evidence for linkage of autism susceptibility loci and demonstrate evidence for a susceptibility locus at 7q.

1.3.75. Alarcon, M., Cantor, Rm., Liu, J., Gilliam, T.C., Geschwind, D.H. "Evidence for a language quantitative trait locus on chromosome 7q in multiplex autism families." *Am J Hum Genet* 2002 Jan, 70(1) 60-71.

Autism Genetic Research Exchange Consortium.

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Autism is a syndrome characterized by deficits in language and social skills and by repetitive behaviors we hypothesized that potential quantitative trait loci (QTLs) related to component autism endophenotypes might underlie putative or significant regions of autism linkage. We performed nonparametric multipoint linkage analyses, in 152 families from the Autism Genetic Resource Exchange, focusing on three traits derived from the Autism Diagnostic Interview 'age at first word 'age at first phrase; and a composite measure of repetitive and stereotyped behaviour. Families were genotyped for 335 markers and multipoint sib pair linkage analyses were conducted. Using nonparametric multipoint linkage analysis, we found the strongest QTL evidence for age at first word on chromosome 7q (nonparametric test statistic (Z) 2.98;p=001), and subsequent linkage analyses of additional markers and association analyses in the same region supported the initial result (Z=2.85, P=002; chi(2)=18.84, df 8, p=016). Moreover, the peak fine mapping result for repetitive behavior (Z=2.481;P=007) localized to a region overlapping this language QTL. The putative autism susceptibility locus on chromosome 7 may be the result of separate QTLs for the language and repetitive or stereotyped behavior deficits that are associated with the disorder.

1.3.76. el-Hazmi, M.A. "Autism and mental retardation: the genetic relationship and contribution." *East Mediterr Health J.* 2001 May;7(3):536-43. Publication Types: Review, Review, Tutorial.

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Autism, a neurodevelopmental disorder first described in 1943, is reviewed. The signs and symptoms of the disorder are described together with the etiological factors. The evidence for a genetic etiology of autism and its association with other genetic disorders are discussed. Possible candidate genes for autism are described.

1.3.77. Menold, M.M., Shao, Y., Wolpert, C.M., Donnelly, S.L., Raiford, K.L., Martin, E.R., Ravan, S.A., Abramson, R.K., Wright, H.H., Delong, G.R., Cuccaro, M.L., Pericak-Vance, M.A., Gilbert, J.R. "Association analysis of chromosome 15 gabaa receptor subunit genes in autistic disorder." *J Neurogenet* 2001;15(3-4):245-59.

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Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain, acting via the GABAA receptors. The GABAA receptors are comprised of several different homologous subunits, forming a group of receptors that are both structurally and functionally diverse. Three of the GABAA receptor subunit genes (GABRB3, GABRA5 and GABRG3) form a cluster on chromosome 15q11-q13, in a region that has been genetically associated with autistic disorder (AutD). Based on these data, we examined 16 single

nucleotide polymorphisms (SNPs) located within GABRB3, GABRA5 and GABRG3 for linkage disequilibrium (LD) in 226 AutD families (AutD patients and parents). Genotyping was performed using either OLA (oligonucleotide ligation assay), or SSCP (single strand conformation polymorphism) followed by DNA sequencing. We tested for LD using the Pedigree Disequilibrium Test (PDT). PDT results gave significant evidence that AutD is associated with two SNPs located within the GABRG3 gene (exon5_539T/C, $p=0.02$ and intron5_687T/C, $p=0.03$), suggesting that the GABRG3 gene or a gene nearby contributes to genetic risk in AutD.

1.3.78. Purcell, A.E., Jeon, O.H., Pevsner, J. "The abnormal regulation of gene expression in autistic brain tissue." *J Autism Dev Disord* 2001 Dec;31(6):545-9.

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Autism is a pervasive developmental disorder of unknown etiology. It is likely caused by mutations in one or more genes. One approach to understanding the molecular changes that occur in autism is to measure gene expression in post-mortem brain samples from individuals diagnosed with autism. This may be accomplished with techniques such as cDNA microarrays or subtractive hybridization. In general, gene expression is regulated as a function of body region, developmental time, and physiological state. A premise of the approaches we describe is that gene expression is regulated in cells from autistic individuals as a consequence of the disease process. It may be useful to detect such changes in order to identify selective biological markers for autism. Additionally, the abnormal regulation of gene expression may reveal cellular pathways that have been disrupted, suggesting strategies for therapeutic intervention.

1.3.79. Collaborative Linkage Study of Autism. "An autosomal genomic screen for autism." *Am J Med Genet* 2001 Dec 8;105(8):609-15.

Autism is a severe neurodevelopmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are detectable in early childhood. The etiology of idiopathic autism is strongly genetic, and oligogenic transmission is likely. The first stage of a two-stage genomic screen for autism was carried out by the Collaborative Linkage Study of Autism on individuals affected with autism from 75 families ascertained through an affected sib-pair. The strongest multipoint results were for regions on chromosomes 13 and 7. The highest maximum multipoint heterogeneity LOD (MMLS/het) score is 3.0 at D13S800 (approximately 55 cM from the telomere) under the recessive model, with an estimated 35% of families linked to this locus. The next highest peak is an MMLS/het score of 2.3 at 19 cM, between D13S217 and D13S1229. Our third highest MMLS/het score of 2.2 is on chromosome 7 and is consistent with the International Molecular Genetic Study of Autism Consortium report of a possible susceptibility locus somewhere within 7q31-33. These regions and others will be followed up in the second stage of our study by typing additional markers in both the original and a second set of identically ascertained autism families,

which are currently being collected. By comparing results across a number of studies, we expect to be able to narrow our search for autism susceptibility genes to a small number of genomic regions.

1.3.80. Collaborative Linkage Study of Autism. "Incorporating language phenotypes strengthens evidence of linkage to autism." *Am J Med Genet* 2001 Dec 8;105(8):539-47.

We investigated the effect of incorporating information about proband and parental structural language phenotypes into linkage analyses in the two regions for which we found the highest signals in our first-stage affected sibling pair genome screen: chromosomes 13q and 7q. We were particularly interested in following up on our chromosome 7q finding in light of two prior reports of linkage of this region to developmental language disorder, since one of the diagnostic criteria for autism is absent or abnormal language development. We hypothesized that if the language phenotype were genetically relevant to linkage at the chromosome 7q locus, then incorporating parents phenotypes would increase the signal at that locus, and most of the signal would originate from the subset of families in which both probands had severe language delay. The results support these hypotheses. The linkage signals we obtained on chromosome 7q as well as at least one signal on chromosome 13q are mainly attributable to the subgroup of families in which both probands had language delay. This became apparent only when the parents' history of language-related difficulties was also incorporated into the analyses. Although based on our data, we were not able to distinguish between epistasis or heterogeneity models, we tentatively concluded that there may be more than one autism susceptibility locus related to language development.

1.3.81. Collaborative Linkage Study of Autism. "An autosomal genomic screen for autism". *Am J Med Genet* 2001 Dec 8; 105 (8):609-15.

Autism is a severe neurodevelopmental disorder defined by social and communication deficits and ritualistic-repetitive behaviours that are detectable in early childhood. The etiology of idiopathic autism is strongly genetic, and oligogenic transmission is likely. The first stage of a two-stage genomic screen for autism was carried out by the Collaborative Linkage Study of Autism on individuals affected with autism from 75 families ascertained through an affected sib-pair. The strongest multipoint results were for regions on chromosomes 13 and 7. The highest maximum multipoint heterogeneity LOD (MMLS/het) score is 3.0 at D13S800 (approximately 55 cM, between D13S217 and D13S1229. Our third highest MMLS/het scores of 2.2 is on chromosome 7 and is consistent with the International Molecular Genetic Study of Autism Consortium report of a possible susceptibility locus somewhere within 7q31-33. These regions and others will be followed up in the second stage of our study by typing additional markers in both the original and a second set of identically ascertained autism families, which are currently being collected. By comparing results across a number of studies, we expect to be able to narrow our search for autism susceptibility genes to a small number of genomic regions.

1.3.82. Collaborative Linkage Study of Autism. **"Incorporating language phenotypes strengthens evidence of linkage to autism."** *Am J Med Genet* 2001 Dec 8, 105(8): 539-47.

We investigated the effect of incorporating information about proband and parental structural language phenotypes into linkage analyses in the two regions for which we found the highest signals in our first-stage affected sibling pair genome screen: chromosomes 13q and 7q. We were particularly interested in following up on our chromosome 7q finding in light of two prior reports of linkage of this region to developmental language disorder, since one of the diagnostic criteria for autism is absent or abnormal language development. We hypothesized that if the language phenotype were genetically relevant to linkage at the chromosome 7q locus, then incorporating parents phenotypes would increase the signal at that locus, and most of the signal would originate from the subset of families in which both probands had severe language delay. The results support these hypotheses. The linkage signals we obtained on chromosome 7q as well as at least one signal on chromosome 13q are mainly attributable to the subgroup of families in which both probands had language delay. This became apparent only when the parents' history of language-related difficulties was also incorporated into the analyses. Although based on our data, we were not able to distinguish between epistasis or heterogeneity models, we tentatively concluded that there may be more than one autism susceptibility locus related to language development.

1.3.83. Tentler, D., Brandberg, G., Betancur, C., Gillberg, C., Anneren, G., Orsmark, C., Green, E.D., Carlsson, B., Bahl, N. **"A balanced reciprocal translocation t(5;7) (q14;q32) associated with autistic disorder: molecular analysis of the chromosome 7 breakpoint."** *AM J Med Genet* 2001 Dec 8;105(8) : 729-36.

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Autism is a neuropsychiatric disorder characterized by impairments in social interaction, restricted and stereotypic pattern of interest with onset by 3 years of age. The results of genetic linkage studies for autistic disorder (AD) have suggested a susceptibility locus for the disease on the long arm of chromosome 7. We report a girl with AD and a balanced reciprocal translocation t(5;7) (q14;q32). The mother carries the translocation but does not express the disease. Fluorescent in situ hybridization (FISH) analysis with chromosome 7-specific YAC clones showed that the breakpoint coincides with the candidate region for AD. We identified a PAC clone that spans the translocation breakpoint and the breakpoint was mapped to a 2 kb region. Mutation screening of the genes SSBP and T2R3 located just centromeric to the breakpoint was performed in a set of 29 unrelated autistic sibling pairs who shared at least one chromosome 7 haplotype. We found no sequence variations, which predict amino acid alterations. Two single nucleotide polymorphisms were identified in the T2R3 gene, and associations between allele variants and AD in our

population were not found. The methylation pattern of different chromosome 7 regions in the patient's genomic DNA appears normal. Here we report the clinical presentation of the patient with AD and the characterization of the genomic organization across the breakpoint at 7q32. The precise localization of the breakpoint on 7q32 may be relevant for further linkage studies and molecular analysis of AD in this region. Copyright 2001 Wiley-Liss, Inc.

1.3.84. Bolton, P.F., Dennis, N.R., Browne, C.E., Thomas, N.S., Veltman, M.W., Thompson, R.J., Jacobs, P. **"The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders."** *Am J Med Genet* 2001 Dec 8; 105(8): 675-85. *Publication Types: Review, Review of Reported Cases.*

Section of developmental Psychiatry, University of Cambridge, Cambridge, UK.

This study investigated the phenotypic manifestations of interstitial duplications of chromosome 15 that involve the Prader-Willi/Angleman syndrome critical region (PWACR). Twenty-one affected individuals from six families were evaluated in detail, using standardized and semi-standardized measures of intelligence, psychopathology, and physical anomalies. Special attention was placed on determining the prevalence of autism spectrum disorders as well as the relationship between the parental origin of the duplication and the phenotypic effects. Assessments of the affected individuals were compared with evaluations of the unaffected relatives from the same families. Results indicated that duplications in the region were associated with variable degrees of intellectual impairments and motor coordination problems. Four of the subjects received a diagnosis of pervasive developmental disorder. Three of these cases were probands and only one met criteria for classic autism. There was very little evidence of the duplication cosegregating with autism spectrum disorder diagnosis. Paternally inherited duplications were significantly less likely to give rise to developmental delay but not necessarily autism spectrum disorders. They also suggest that phenotypic expression is dependent on the parental origin of the duplication and implicate maternally active genes in the pathogenesis of the developmental impairments. Further research will be required to clarify the range and basis of the phenotypic manifestations. Copyright 2001 Wiley-Liss, Inc.

1.3.85. Chibuk, T.K., Bischof, J.M., Wevrick, R. **"A novel MAGE-like gene in the chromosome 15 autism susceptibility region: expression, imprinting, and mapping of the human and mouse orthologues."** *BMC Genet* 2001;2(1):22.

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BACKGROUND: Proximal chromosome 15q is implicated in neurodevelopmental disorders including Prader-Willi and Angelman syndromes, autistic disorder and developmental abnormalities resulting from chromosomal deletions or duplications. A subset of genes in this region are subject to

genomic imprinting, the expression of the gene from only one parental allele. RESULTS We have now identified the NDNL2 (also known as MAGE-G) gene within the 15q autistic disorder susceptibility region and have mapped its murine homolog to the region of conserved synteny near necdin (Ndn) on mouse Chr 7. NDNL2/IMAGE_G is a member of a large gene family that includes the x-linked MAGE cluster, MAGED 1 (NRAGE), MAGEL2 and NDN, where the latter two genes are implicated in Prader-Willi syndrome. We have now determined that NDNL2/Ndn2 is widely expressed in mouse and human fetal and adult tissues, and that it is apparently not subject to genomic imprinting by the PWS/AS Imprinting Centre. CONCLUSION: Although NDNL2/MAGE-G in the broadly defined chromosome 15 autistic disorder susceptibility region, it is not likely to be pathogenic based on its wide expression pattern and lack of imprinted expression.

1.3.86. Rogers, S.J., Wehner, D.E., Hagerman, R. "The behavioural phenotype in fragile X : symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders." *J Dev Behav Pediatr* 2001 Dec; 22(6): 409-17.

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This study was designed to explore the behavioural phenotype of autism in a group of young children with fragile X syndrome (FXS). Twenty-four children with FXS, ages 21 to 48 months, were compared with two well-matched groups : 27 children with autism (AD) and 23 children with other developmental delays (DD), on two standardized autism instruments, as well as on measures of development and adaptive behaviour. Two FXS subgroups emerged. One subgroup (n=16) did not meet study criteria for autism. Their profiles on the autism instruments and the developmental instruments were virtually identical to the other DD group. The other FXS subgroup (n=8, 33% of the total DXFs group) met study criteria for autism. Their profiles on the autism instruments were virtually identical to the group with autism. The finding of two FXS subgroups raises a hypothesis of additional genetic influences in the FXS autism group, warranting genetic studies.

1.3.87. Spence, M.A. "The Genetics of autism." *Curr Opin Pediatr* 2001 Dec; 13(6) : 561-5. Publication Types: Review, Review, Tutorial.

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Autism is a significant childhood disorder. Studies are underway to define more clearly the disorder and its various manifestations and to correlate this information with an etiology. Genes are known to play an important role in autism, and a vigorous search is underway to define those genes. The Human Genome Project provides the basis that allows us to move beyond single gene disorders and to contemplate progress for complex disorders, such as autism. Genome screens of affected siblings and detailed molecular analyses of chromosome abnormalities identified in autistic subjects

has led in the past year to the identification of several candidate genes. However, the problem of determining which are the real genes remains. This is complicated because the presentation of the disorder is so variable, and milder manifestations in relatives are not yet understood. But the fact that we can now name possible genes for this order reflects how quickly our understanding is progressing.

1.3.88. Folstein, S.E., Rosen-Sheidley, B. "Genetics of autism: complex aetiology for a heterogeneous disorder." *Nat Rev Genet* 2001 Dec;(12) : 943-55. Publication Types: Review, Review, Academic.

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Since autism was first recognized as a disorder in 1943, speculation about its aetiology has ranged from biological to Psychological and back again. After twin studies during the 1970s and 1980s yielded unequivocal evidence for a genetic component, aetiological research in autism began to focus primarily on uncovering the genetic mechanisms involved. The identification of chromosomal abnormalities and Mendelian syndromes among individuals with autism, in conjunction with data from genome screens and candidate gene studies, has helped to refine the view of the complex genetics that underlines autism spectrum conditions.

1.3.89. Roubetie, A., Semprino, M., Chaze, A.M., River, F., Humbertclaude, V., Cheminal, R., Lefort, G., Echenne, B. "Neurological presentation of three patients with 22q11 deletion (CATCH 22 syndrome)." *Brain Dev* 2001 Dec;23(8):810-4.

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Chromosome 22q11 deletion (CATCH 22 syndrome or velocardiofacial syndrome) is one of the most frequent chromosomal syndromes. Neurological features other than cognitive disorders are probably the least-described part of the expanding phenotype of the 22q11 deletion. We report the neurological features of three unrelated children with a de novo deletion: one patient with an autistic disorder, a second patient with hypocalcaemic neonatal seizures and unusual persistent epileptic focus at electroencephalographic follow-up, and a third patient with atypical absence epilepsy. These observations enlarge the clinical and neurological spectrum of the 22q11 deletion. Awareness of such cases is necessary, and a diagnosis of the 22q11 deletion should be suspected in children with common neurological feature associated with severe or mild dysmorphism. Diagnosis of the 22q11 deletion should be confirmed by fluorescence in situ hybridization analysis associated with standard chromosomal analysis.

1.3.90. Park, R.J., Bolton, P.F. "Pervasive developmental disorder and obstetric complications in children and adolescents with tuberous sclerosis." *Autism* 2001 Sep; 5(3):237-48.

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Children with autism have an increased risk for obstetric complications but it is not known whether these are of primary aetiological significance. It is also unclear whether obstetric complications play a secondary role in shaping phenotypic expression in individuals at genetic risk for autism. We investigated this question by studying the role of obstetric complications in determining phenotypic manifestations in tuberous sclerosis, a single gene disorder frequently associated with autism spectrum disorders. Obstetric histories of 43 children with non-familial TS and 40 unaffected siblings were obtained using a structured parent interview. ADI-R, ADOS-G and IQ evaluations were undertaken. Children with TS experienced more obstetric complications than their unaffected siblings, but these were related to mild rather than severe adversities. No difference in obstetric complications were found in children with and without autism spectrum disorders and there was no positive correlation between obstetric adversities and severity of autism spectrum disorders or intellectual impairments.

1.3.91. Cheung J., Petek, E., Nakabayashi, K., Tsui, L.C., Vincent, J.B., Scherer, S.W. "**Identification of the human cortactin-binding protein-2 gene from the autism candidate region at 7q31.**" *Genomics* 2001 Nov; 78(1-2):7-11.

Department of Genetics, The Hospital for Sick children, University of Toronto, Toronto, Ontario, M5G 1X8, Canada.

Human chromosome 7q31 contains putative susceptibility loci for autism (AUTSI) and speech and language disorder (SPCH1). We report here the identification and characterization of a novel gene encoding cortactin-binding protein-2 (CORTBP2), which is located 45 kb telomeric to the cystic fibrosis transmembrane conductance regulator gene (CFTR) at 7q31.3. The full-length (5975-bp) gene was isolated and found to be composed of 2.3 exons encompassing 170kb of DNA. In addition to being a positional candidate for AUTSI, CORTBP2 was expressed at a highest levels in the brain, as shown by northern blot analysis. Subsequent mutation analysis of CORTBP2 in 90 autistic patients identified two polymorphisms, including a leucine to valine change caused by a T to C substitution in exon 15. However, comparison of allele frequencies between autistic and control populations (n=96) showed no significant difference, suggesting that this variant is not a susceptibility factor for autism.

1.3.92. Smith, M., Escamilla, J.R., Filipek, P., Bocian, M.E., Modahl, C., Flodman, P., Spence, M.A. "**Molecular genetic delineation of 2q37.3 deletion in autism and osteodystrophy: report of a case and of new markers for deletion screening by PCR.**" *Cytogenet Cell Genet* 2001;94(1-2):15-22.

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We recently studied a patient who meets criteria for autistic disorder and has a 2q37 deletion. Molecular cytogenetic studies

were carried out using DNA isolated from 22 different 2q37 mapped BACs to more precisely define the extent of the chromosome deletion. We also analyzed 2q37 mapped polymorphic markers. In addition DNA sequences of BACs in the deletion region were scanned to identify microsatellite repeat markers in the 2q37.3 region. These markers enabled us to determine the parental origin of the deletion in our patient. DNA from 8-13 unrelated individuals was used to determine heterozygosity estimates for these markers. We review four genes deleted in our patient - genes whose known functions and sites of expression in the brain and/or bone make them candidates for involvement in autism and/or the osteodystrophy observed in patients with 2q37.3 deletions.

1.3.93. Hessel, D., Dyer-Friedman, J., Glaser, B., Wisbeck, J., Barajas, R.G., Taylor, A., Reiss, A.L. "**The influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with fragile X syndrome.**" *Pediatrics* 2001 Nov; 108(5):L88.

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California 94305-5719, USA.

OBJECTIVE: Fragile X syndrome, caused by mutations in a single gene of the X chromosome (FMR1), is associated with neurobehavioral characteristics including social deficits with peers, social withdrawal, gaze aversion, inattention, hyperactivity, anxiety, depression, and autistic behavior. However, there is considerable variability in the behavioral and psychiatric problems among children with this condition. The purpose of this study was to measure genetic and environmental factors influencing behavior problems and autistic symptoms in children with fragile X syndrome. **DESIGN:** We conducted an in-home evaluation of 120 children (80 boys and 40 girls) with the fragile X full mutation and their unaffected siblings, including measurements of the FMR1 protein (FMRP). **METHODS:** We performed a single-blinded, prospective, open-label trial by conducting formal language testing and blinded behavioral rating both before and repeatedly after a standardized infusion of secretin. We selected autistic children who were similar in age and profile to those described in the published retrospective case review. Inclusion criteria for study participation included age (3-6 years), confirmed diagnosis of autism, and reported gastrointestinal symptoms (16 had chronic diarrhea, 2 had gastroesophageal reflux, and 2 had chronic constipation). Twenty children (18 male) were admitted to the Pediatric Clinical Research Centre at the University of California, San Francisco after administration of the Preschool Language Scale-3 (PLS-3). A 3 CU/kg dose of secretin (Secretin-Ferring) was administered intravenously (upper endoscopy was not performed). Behavioral ratings were derived using the Autism Observation Scale applied to a 30-minute time sample of the child's behavior consisting of a videotape of the PLS-3 (structured setting) and a second free play session with a standard set of developmentally appropriate toys. Participants then returned for follow-up evaluations, with readministrations of the PLS-3 at 1, 2, 3, and 5 weeks postinfusion, and videotaping of each session for later blinded

review by 2 independent observers using the Autism Observations Scale, uninformed about week of posttreatment. We also surveyed parents of our study children about their impressions of the effects of secretin using a 5-point Likert scale for parents to rate changes seen in their child. RESULTS: with a total study completion rate across all participants of 96%, repeated measures analysis of variance revealed no significant increases in children's language skills from baseline across all 5 study time periods after a single infusion of secretin. Similarly, neither significant decreases in a typical behaviors nor increases in prosocial behaviors and developmentally appropriate play skills emerged. Furthermore, no relationship was found between parental reports of change and observable improvement in the sample. Despite the objective lack of drug effect, 70% of parents in our study reported moderate to high change in their child's language and behavior. Furthermore, 85% of parents reported that they felt that their child would obtain at least some additional benefits from another infusion of secretin.

CONCLUSIONS : The results of our pilot study indicate that intravenous secretin had no effects in a 5-week period on the language and behavior of 29 children with autism and gastrointestinal symptoms. The open-label, prospective design of our study with blinded reviews of patients both and after secretin administration follows the scientific method by seeking to reproduce an observed phenomenon using validating and reliable outcome measures. Pilot studies remain a mandatory step for the design of future randomized, clinical trials investigating potential treatments for children with autism.

1.3.94. Greenberg, D.A., Hodge, S.E., Sowinski, J., Nicoll, D. **"Comment in: Excess of twins among affected sibilings pairs with autism : implications for the etiology of autism."** *Am J Hum Genet* 2001 Nov; 69(5) : 1062-7.

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It is widely accepted that genes play a role in the etiology of autism. Evidence for this derives, in part, from twin data. However, despite converging evidence from gene-mapping studies, aspects of the genetic contribution remain obscure. In a sample of families selected because each had exactly two affected sibs, we observed a remarkably high proportion of affected twin pairs, both MZ and DZ. Of 166 affected sib pairs, 30 (12 MZ, 17 DZ, and 1 of unknown zygosity) were twin pairs. Deviation from expected values. We demonstrate that to ascribe the excess of twins with autism solely to ascertained sample of individuals with type I diabetes, there was no deviation from expected values. We demonstrate that to ascribe the excess of twins with autism solely to ascertainment bias would require very large ascertainment factors; for example, affected twin pairs would need to be, on average, approximately 10 times more likely if "stoppage" plays a role. Either risk factors (related to twinning or to fetal development) or other factors (genetic or nongenetic) in the parents may contribute to autism.

1.3.95. Davies, W., Isles, A.R., Wilkinson, L.S. **"Imprinted genes and mental dysfunction."** *Ann Med* 2001 Sep; 33(6) : 428-36.

Neurobiology and Developmental Genetics Programmes, The Babraham Institute, Cambridge, UK.

There is a rapidly accumulating body of evidence from family, adoption and twin studies suggestive of a genetic component to many common mental disorders. In some cases, the transmission of abnormalities has been shown to be dependent upon the sex of the parent from whom they are inherited. Such parent-of-origin effects may be explained by a number of genetic mechanisms, one of which is 'genomic imprinting'. In imprinted genes one allele is silenced according to its parental origin. This in turn means that imprinted traits are passed down the maternal or paternal line, in contrast to the more frequent Mendelian mode of inheritance that is in different to the parental origin of the allele. In the present review, we survey the evidence for the influence of imprinted conditions, where in some cases abnormalities have been mapped to particular gene candidates, to examples where the evidence for parent-of-origin effects is less strong. We also consider, briefly, the wider implications of imprinted effects on mental dysfunction, in particular with respect to evolutionary pressures on mammalian brain development and function.

1.3.96. Bradford, Y., Haines, J., Hutcheson, H., Gardiner, M., Braun, T., Sheffield, V., Cassavant, T., Huang, W., Wang, K., Vieland, V., Folstein, S., Santangelo, S., Piven, J. **"Incorporating language phenotypes strengthens evidence of linkage to autism."** *Am J Med Genet* 2001 Aug 8; 105(6):539-47.

Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee, USA.

We investigated the effect of incorporating information about proband and parental structural language phenotypes into linkage analyses in the two regions for which we found the highest signals in our first-stage affected sibling pair genome screen: chromosomes 13q and 7q. We were particularly interested in following up on our chromosome 7q finding in light of two prior reports of linkage of this region to developmental language disorder, since one of the diagnostic criteria for autism is absent or abnormal language development. We hypothesized that if the language phenotype were genetically relevant to linkage at the chromosome 7q locus, then incorporating parents phenotypes would increase the signal at that locus, and most of the signal would originate from the subset of families in which both probands had severe language delay. The results support these hypotheses. The linkage signals we obtained on chromosome 7q as well as at least one signal on chromosome 13q are mainly attributable to the subgroup of families in which both probands had language delay. This became apparent only when the parents' history of language-related difficulties was also incorporated into the analyses. Although based on our data, we were not able to distinguish between epistasis or heterogeneity models, we tentatively concluded that there may be more than one

autism susceptibility locus related to language development. Copyright 2001 Wiley-Liss, Inc.

1.3.97. Goffin, A., Hoefsloot, L.H., Bosgoed, F., Swillen, A., Fryns, J.P. "PTEN mutation in a family with Cowden syndrome and autism." *Am J Med Genet* 2001 Aug 8;105(6):521-4.

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We report on a mother and son with Cowden syndrome and a PTEN mutation. The boy also exhibits autistic behavior and mental retardation, while his mother has a normal intelligence and social interaction pattern. We review the scanty literature data on the association of Cowden syndrome and autism and emphasize that the association of progressive macrocephaly and pervasive developmental disorder seems to be an indication for screening for PTEN mutations. Copyright 2001 Wiley-Liss, Inc.

1.3.98. Torres, A.R., Maciulis, A., Odell, D. "The association of MHC genes with autism." *Front Biosci* 2001 Aug 1;6:D936-43. Publication Types: Review, Review, Tutorial.

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Several immune abnormalities have been noted in autistic subjects. These associations have been extended to the Major Histocompatibility Complex (MHC), a section of DNA remarkable for the number of encoded proteins with immunological functions. The strongest MHC association identified thus far is for the null allele of C4B in the class III region. The complex allelic composition of C4 as determined by immunoelectrophoresis is discussed. Low levels of C4 resulting from the null allele may be important in disease pathogenesis especially since C4 has been identified in developing brain neurons. The DNA region just telomeric to C4 has several genes including tumor necrosis factor which encode proteins with immunological functions. These proteins may act in concert with C4 in disease contribution and the genes should be more closely examined.

1.3.99. Asherson, P.J., Curran, S. "Approaches to gene mapping in complex disorders and their application in child psychiatry and psychology." *Br J Psychiatry* 2001 Aug;179:122-8. Publication Types: Review, Review, Tutorial.

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BACKGROUND: Twin studies demonstrate the importance of genes and environment in the aetiology of childhood psychiatric and neurodevelopmental disorders. Advances in molecular genetics enable the identification of genes involved in complex disorders and enable the study of molecular mechanisms and gene-environment interactions. **AIMS:** To review the role of molecular genetics studies in childhood behavioural and developmental traits. **METHOD:** Molecular approaches to complex disorders are reviewed, with examples

from autism, reading disability and attention-deficit hyperactivity disorder (ADHD). **RESULTS:** The most robust finding in ADHD is the association of a variable number tandem repeat polymorphism in exon 3 of the DRD4 gene. Other replicated associations with ADHD are outlined in the text. In autism, there is a replicated linkage finding on chromosome 7. Linkage studies in reading disability have confirmed a locus on chromosome 6 and strongly suggest one on chromosome 15. **CONCLUSIONS:** In the next 5-10 years susceptibility genes for these disorders will be established. Describing their relationship to biological and behavioural function will be a far greater challenge.

1.3.100. "A genomewide screen for autism: strong evidence for linkage to chromosomes 2q, 7q, and 16p." *Am J Hum Genet* 2001 Sep;69(3):570-81.

International Molecular Genetic Study of Autism Consortium (IMGSAC).

Autism is characterized by impairments in reciprocal communication and social interaction and by repetitive and stereotyped patterns of activities and interests. Evidence for a strong underlying genetic predisposition comes from twin and family studies, although susceptibility genes have not yet been identified. A whole-genome screen for linkage, using 83 sib pairs with autism, has been completed, and 119 markers have been genotyped in 13 candidate regions in a further 69 sib pairs. The addition of new families and markers provides further support for previous reports of linkages on chromosomes 7q and 16p. Two new regions of linkage have also been identified on chromosomes 2q and 17q. The most significant finding was a multipoint maximum LOD score (MLS) of 3.74 at marker D2S2188 on chromosome 2; this MLS increased to 4.80 when only sib pairs fulfilling strict diagnostic criteria were included. The susceptibility region on chromosome 7 was the next most significant, generating a multipoint MLS of 3.20 at marker D7S477. Chromosome 16 generated a multipoint MLS of 2.93 at D16S3102, whereas chromosome 17 generated a multipoint MLS of 2.34 at HTTINT2. With the addition of new families, there was no increased allele sharing at a number of other loci originally showing some evidence of linkage. These results support the continuing collection of multiplex sib-pair families to identify autism-susceptibility genes.

1.3.101. Beyer, K.S., Klauck, S.M., Wiemann, S., Poustka, A. "Construction of a physical map of an autism susceptibility region in 7q32.3-q33." *Gene* 2001 Jul 11;272(1-2):85-91.

Department of Molecular Genome Analysis, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.

The fast evolving progress of the human genome mapping and sequencing efforts facilitate the detection of genes also for complex traits. We focus on the detection of susceptibility loci for autism, a prototypical pervasive developmental disorder. Five genome screens worldwide have identified several putative locations of susceptibility genes thus far, with the most common region on chromosome 7q. In order to

identify new candidate genes for infantile autism we constructed a physical map of bacterial artificial chromosome, P1-derived artificial chromosome and yeast artificial chromosome clones of a 3 Mb region between D7S1575 and D7S500, including a complete contig of the approximately 1.2 Mb region around D7S2533, the marker with the most significant association result. We developed 16 novel sequence tag sites and mapped 23 genes/expressed sequence tags to the contigs. As this map contains a putative autistic disorder locus this integrated physical and transcript map provides a valuable resource for identification of candidate gene(s).

1.3.102. Vourc'h, P., Bienvenu, T., Beldjord, C., Chelly, J., Barthelemy, C., Muh, J.P., Andres, C. "No mutations in the coding region of the Rett syndrome gene MECP2 in 59 autistic patients." *Eur J Hum Genet* 2001 Jul;9(7):556-8.

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Autistic disorder is a pervasive developmental disorder considered to have a multigenic origin. Mental retardation is present in 75% of autistic patients. Autistic features are found in Rett syndrome, a neurological disorder affecting girls and associated with severe mental retardation. Recently, the gene responsible for the Rett syndrome, methyl CpG-binding protein (MECP2) gene, was identified on the X chromosome by a candidate gene strategy. Mutations in this gene were also observed in some mentally retarded males. In this study we tested MECP2 as a candidate gene in autistic disorder by a DGGE analysis of its coding region and intron-exon boundaries. Among 59 autistic patients, 42 males and 17 females, mentally retarded or not, no mutations or polymorphisms were present in the MECP2 gene. Taking into account the size of our sample, we conclude that MECP2 coding sequence mutations are not an important factor (less than 5% of cases) in the aetiology of autistic disorder.

1.3.103. Shevell, M.I., Majnemer, A., Rosenbaum, P., Abrahamowicz, M. "Etiologic yield of autistic spectrum disorders: a prospective study." *J Child Neurol* 2001 Jul;16(7):509-12.

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At present, the etiologic yield in community-derived samples of young children with an autistic spectrum disorder is not known. To address this question, all young children (under 5 years of age) referred for an initial assessment to ambulatory pediatric neurology or developmental pediatric clinics at a tertiary university center over an 18-month period for a suspected developmental delay were prospectively identified. Specific diagnostic testing was left to the discretion of the evaluating physician. In all, 50 children with an autistic spectrum disorder were assessed. Detailed history or physical examination was informative with respect to suggesting the possibility of an underlying etiology in a minority (10/50,20%). Genetic studies (FMR-1, karyotype), electroencephalography (EEG), and neuroimaging were carried out in a majority (42/

50, 34/50, and 33/50, respectively) of the children, for the most part on a screening rather than an indicated basis (31/42, 34/34, and 28/33, respectively). Etiologic yield was low (1/50, 2%), with only a single child identified with a possible Landau-Kleffner variant on sleep EEG tracing. The results suggest an evaluation paradigm with reference to etiologic determination for young children with autistic spectrum disorder that does not presently justify metabolic or neuroimaging on a screening basis. Recurrence risk and treatment implications, however, suggest that strong consideration be given to genetic (FMR-1, karyotype) testing and EEG study despite a relatively low yield.

1.3.104. Liu, J., Nyholt, D.R., Magnussen, P., Parano, E., Pavone, P., Geschwind, D., Lord, C., Iversen, P., Hoh, J., Ott, J., Gilliam, T.C. "A genome-wide screen for autism susceptibility loci." *Autism Genetic Resource Exchange Consortium*.

Am J Hum Genet 2001 Aug;69(2):327-40.

Columbia Genome Center and Department of Psychiatry, Columbia University, New York, NY 10032, USA.

We report the analysis of 335 microsatellite markers genotyped in 110 multiplex families with autism. All families include at least two "affected" siblings, at least one of whom has autism; the remaining affected sibs carry diagnoses of either Asperger syndrome or pervasive developmental disorder. Affected sib-pair analysis yielded multipoint maximum LOD scores (MLS) that reach the accepted threshold for suggestive linkage on chromosomes 5, X, and 19. Nominal evidence for linkage (point-wise $P < .05$) was obtained on chromosomes 2, 3, 4, 8, 10, 11, 12, 15, 16, 18, and 20, and secondary loci were found on chromosomes 5 and 19. Analysis of families sharing alleles at the putative X chromosomal linked locus and one or more other putative linked loci produced an MLS of 3.56 for the DXS470-D19S174 marker combination. In an effort to increase power to detect linkage, scan statistics were used to evaluate the significance of peak LOD scores based on statistical evidence at adjacent marker loci. This analysis yielded impressive evidence for linkage to autism and autism-spectrum disorders with significant genome-wide P values $< .05$ for markers on chromosomes 5 and 8 and with suggestive linkage evidence for a marker on chromosome 19.

1.3.105. Steele, M.M., Al-Adeimi, M., Siu, V.M., Fan, Y.S. "Brief report: A case of autism with interstitial deletion of chromosome 13." *J Autism Dev Disord* 2001 Apr;31(2):231-4.

Department of Psychiatry, University of Western Ontario, London Health Sciences Centre, Canada. margaret.steele@lhsc.on.ca

A case of an 18-year-old male who meets the DSM-IV criteria for autistic disorder and borderline intelligence is described. Cytogenetic evaluation revealed a karyotype of 46, XY, del(13)(q14q22). The relevance of this case to the etiology of autism is discussed.

1.3.106. Wassink, T.H., Piven, J., Vieland, V.J., Huang, J., Swiderski, R.E., Pietila, J., Braun, T., Beck, G., Folstein, S.E., Haines, J.L., Sheffield, V.C. "Evidence supporting WNT2 as an autism susceptibility gene." *Am J Med Genet* 2001 Jul 8;105(5):406-13.

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We examined WNT2 as a candidate disease gene for autism for the following reasons. First, the WNT family of genes influences the development of numerous organs and systems, including the central nervous system. Second, WNT2 is located in the region of chromosome 7q31-33 linked to autism and is adjacent to a chromosomal breakpoint in an individual with autism. Third, a mouse knockout of Dvl1, a member of a gene family essential for the function of the WNT pathway, exhibits a behavioral phenotype characterized primarily by diminished social interaction. We screened the WNT2 coding sequence for mutations in a large number of autistic probands and found two families containing nonconservative coding sequence variants that segregated with autism in those families. We also identified linkage disequilibrium (LD) between a WNT2 3'UTR SNP and our sample of autism-affected sibling pair (ASP) families and trios. The LD arose almost exclusively from a subgroup of our ASP families defined by the presence of severe language abnormalities and was also found to be associated with the evidence for linkage to 7q from our previously published genomewide linkage screen. Furthermore, expression analysis demonstrated WNT2 expression in the human thalamus. Based on these findings, we hypothesize that rare mutations occur in the WNT2 gene that significantly increase susceptibility to autism even when present in single copies, while a more common WNT2 allele (or alleles) not yet identified may exist that contributes to the disorder to a lesser degree. Copyright 2001 Wiley-Liss, Inc.

1.3.107. Plank, S.M., Copeland-Yates, S.A., Sossey-Alaoui, K., Bell, J.M., Schroer, R.J., Skinner, C., Michaelis, R.C. "Lack of association of the (AAAT)6 allele of the GXAlu tetranucleotide repeat in intron 27b of the NF1 gene with autism." *Am J Med Genet* 2001 Jul 8;105(5):404-5.

Presbyterian College, Clinton, South Carolina, USA.

A novel allele of the GXAlu tetranucleotide repeat in intron 27b of the neurofibromatosis 1 (NF1) gene has recently been reported to be present in 4.7% of autistic patients but not in controls. We have found the novel GXAlu allele absent in 204 patients from the South Carolina Autism Project and 200 controls. The autism population studied includes a significant number of patients with hypotonia, stereotyped behaviors, or postural, gait, and motor abnormalities similar to those seen in the patients previously reported to possess the novel GXAlu allele. This suggests that the novel (AAAT)6 GXAlu allele is not associated with autism. Copyright 2001 Wiley-Liss, Inc.

1.3.108. Tordjman, S., Gutknecht, L., Carlier, M., Spitz, E., Antoine, C., Slama, F., Carsalade, V., Cohen, D.J., Ferrari, P., Roubertoux, P.L., Anderson, G.M. "Role of the serotonin transporter gene in the behavioral expression of autism." *Mol Psychiatry* 2001 Jul;6(4):434-9. Publication Types: Multicenter Study.

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The promoter polymorphism of the serotonin transporter gene (HTT, locus SLC6A4) is of special interest in autism given the well-replicated platelet hyperserotonemia of autism, treatment effects of serotonin reuptake inhibitors, and the role of serotonin in limbic functioning and neurodevelopment. Parent-offspring transmission of the long (l) and short (s) alleles of the deletion/insertion polymorphism in the HTT promoter region was examined in families of 71 children with autism using the transmission test for linkage disequilibrium (TDI). Transmission of HTT promoter alleles did not differ between probands with autism and their unaffected siblings. However, allelic transmission in probands was dependent upon severity of impairments in the social and communication domains, with greater s allele transmission in severely impaired individuals and greater l transmission in mild/moderately impaired individuals. This relationship between HTT promoter alleles and severity of autistic impairment was also seen when ratings of social and communication behaviors were compared across genotypes. The data indicate that HTT promoter alleles by themselves do not convey risk for autism, but, rather, modify the severity of autistic behaviors in the social and communication domains. The results require replication and, given the size of the groups and subgroups examined, must be considered still preliminary. The results suggest that future research on the genetics of autism should carefully assess each of the major behavioral domains and seriously consider the possible role of modifying loci.

1.3.109. Lord, C., Leventhal, B.L., Cook, E.H. Jr. "Quantifying the phenotype in autism spectrum disorders." *Am J Med Genet* 2001 Jan 8;105(1):36-8.

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Twin and family studies suggest that familial transmission in autism extends to a spectrum of social and behavioral deficits that characterize individuals who have significant impairments within the autism spectrum, but do not meet formal criteria for autistic disorder. Standardized diagnostic instruments, including the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS-WPS Edition), offer the opportunity to quantify deficits across the autism spectrum, controlling effects of language and cognitive delay, in individuals with significant impairments. It is suggested that quantitative measures of social reciprocity and repetitive behaviors and interests, with separate quantification of expressive language level and nonverbal intelligence, most accurately reflect the range of behavioral phenotypes in autism spectrum disorders.

1.3.110. Piven, J. "The broad autism phenotype: a complementary strategy for molecular genetic studies of autism." *Am J Med Genet* 2001 Jan 8;105(1):34-5

North Carolina Mental Retardation and Developmental Disabilities Research Center, University of North Carolina at Chapel Hill, 27599-7250, USA.

The genetic liability for autism appears to be expressed not only as the full syndrome of autism, but in milder, qualitatively similar characteristics that collectively have been referred to as constituting the broad autism phenotype. Identification of components of the broad autism phenotype that segregate independently in relatives of autistic individuals may provide an index of genes that, when present together, may interact to produce autism. Inclusion of information on the broad autism phenotype in relatives, in linkage studies of autism, may provide a potentially important, complementary approach for detecting the genes causing this condition.

1.3.111. Feng, J., Craddock, N., Jones, I.R., Cook, E.H. Jr, Goldman, D., Heston, L.L., Peltonen, L., DeLisi, L.E., Sommer, S.S. "Systematic screening for mutations in the glycine receptor alpha2 subunit gene (GLRA2) in patients with schizophrenia and other psychiatric diseases." *Psychiatr Genet* 2001 Mar;11(1):45-8.

Department of Molecular Genetics, City of Hope National Medical Center/Beckman Research Institute, Duarte, California 91010-3000, USA.

The glycine receptor, which is a member of the ligand-gated ion channel superfamily, mediates synaptic inhibition in the spinal cord and other brain regions. This superfamily has been implicated in the pathogenesis of schizophrenia and other psychiatric diseases. The complete coding sequence and splice junctions of the GLRA2 gene were scanned by DOVAM-S, a form of SSCP analysis with sufficient redundancy to detect virtually all mutations. Those analyses were performed in 113 patients with schizophrenia, and in pilot studies of patients with bipolar illness, alcoholism, puerperal psychosis, autism, and attention-deficit hyperactivity disorder (533 kb total scanned sequences). We detected three sequence changes in the coding region, all resulting in silent mutations: C894T in exon 5, C1134T in exon 7, and C1476T in exon 9. These do not alter the structure or the expression of the protein. It is unlikely that mutations in the coding region and splice junction of GLRA2 gene are associated with schizophrenia and other psychiatric diseases.

1.3.112. Lauritsen, M., Ewald, H. "The genetics of autism." *Acta Psychiatr Scand* 2001 Jun;103(6):411-27. Publication Types: Review, Review, Tutorial.

Department of Psychiatric Demography, Institute for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Aarhus University Hospital, DK-8240 Risskov, Denmark.

OBJECTIVE: To review systematically the empirical evidence for the involvement of genetic risk factors in infantile autism. **Method:** We aimed at including all relevant papers written in English. We conducted a Medline search in September 2000.

In addition we searched the reference lists of related papers. **RESULTS:** A relatively small number of reports including family and twin studies, comorbidity, cytogenetic and molecular genetic studies were reviewed. **CONCLUSION:** As well family, twin, cytogenetic and molecular genetic studies supported the importance of genetic risk factors in infantile autism. In most individual cases probably at least a few gene variants simultaneously determine the genetic risk. Presently the most interesting chromosome regions concerning the aetiology of autism are chromosomes 7q31-35, 15q11-13 and 16p13.3 which have been suggested by different lines of genetic research.

1.3.113. Asano, E., Kuivaniemi, H., Huq, A.H., Tromp, G., Behen, M., Rothermel, R., Herron, J., Chugani, D.C. "A study of novel polymorphisms in the upstream region of vasoactive intestinal peptide receptor type 2 gene in autism." *J Child Neurol* 2001 May;16(5):357-63.

Department of Pediatrics, Children's Hospital of Michigan and Wayne State University School of Medicine, Detroit 48201, USA.

We investigated the vasoactive intestinal peptide receptor type 2 (VIPR2) gene as a candidate gene for autism. We searched for mutations in the VIPR2 gene in autistic individuals, and 10 novel polymorphisms were identified. Three polymorphisms in the upstream region were studied in detail, and there was no significant difference in the frequencies between the autistic group (n = 14) and unrelated controls (n = 52). The distribution of the genotypes in two of the three polymorphisms differed somewhat between autistic subjects with gastrointestinal problems and those without. Moreover, there was a trend showing a correlation between the genotypes for the third polymorphism and the severity of stereotypical behavior as ranked by the Gilliam Autism Rating Scale. These preliminary results suggest that VIPR2 may have a role in gastrointestinal symptoms and stereotypical behaviors in autism, although a larger collection of samples suitable for transmission disequilibrium tests is necessary to validate the results.

1.3.114. "Further characterization of the autism susceptibility locus AUTS1 on chromosome 7q." *Hum Mol Genet* 2001 Apr 15;10(9):973-82.

International Molecular Genetic Study of Autism Consortium (IMGSAC).

Autism is a neurodevelopmental disorder that usually arises on the basis of a complex genetic predisposition. The most significant susceptibility region in the first whole genome screen of multiplex families was on chromosome 7q, although this linkage was evident only in UK IMGSAC families. Subsequently all other genome screens of non-UK families have found some evidence of increased allele sharing in an overlapping 40 cM region of 7q. To further characterize this susceptibility locus, linkage analysis has now been completed on 170 multiplex IMGSAC families. Using a 5 cM marker grid, analysis of 125 sib pairs meeting stringent inclusion criteria resulted in a multipoint maximum LOD score (MLS)

of 2.15 at D7S477, whereas analysis of all 153 sib pairs generated an MLS of 3.37. The 71 non-UK sib pairs now contribute to this linkage. Linkage disequilibrium mapping identified two regions of association—one lying under the peak of linkage, the other some 27 cM distal. These results are supported in part by findings in independent German and American singleton families.

1.3.115. Yirmiya, N., Pilowsky, T., Nemanov, L., Arbelle, S., Feinsilver, T., Fried, I., Ebstein, R.P. "Evidence for an association with the serotonin transporter promoter region polymorphism and autism." *Am J Med Genet* 2001 May 8;105(4):381-6.

Hebrew University of Jerusalem, Jerusalem, Israel.

We have examined three functional polymorphisms, serotonin transporter promoter region polymorphism (5-HTTLPR), dopamine D4 exon III repeat region (DRD4), and catechol-O-methyltransferase (COMT), in a small family-based design toward identifying candidate genes that confer risk for autism. A significant excess of the long/long 5-HTTLPR genotype was observed (likelihood ratio = 7.18; $P = 0.027$; 2 df; $n = 33$ families) as well as preferential transmission of the long allele of the 5-HTTLPR (TDT chi-square = 5.44; $P < 0.025$; 1 df). No association was observed between the COMT and DRD4 polymorphisms and autism in this sample. Some previous studies have observed linkage between autism and the 5-HTTLPR polymorphism and the current results are similar to those first reported by Klauck et al. [1997: *Hum Genet* 100:224-229; 1997: *Hum Mol Genet* 6:2233-2238]. Additionally, elevated serotonin levels have been consistently found in 30%-50% of autistic patients and may represent a marker for familial autism. Hyperserotonemia in autism appears to be due to enhanced 5-HT uptake, as free 5-HT levels are normal and the current report of an excess of the long/long 5-HTTLPR genotype in autism could provide a partial molecular explanation for high platelet serotonin content in autism. Copyright 2001 Wiley-Liss, Inc.

1.3.116. Bottini, N., De Luca, D., Saccucci, P., Fiumara, A., Elia, M., Porfirio, M.C., Lucarelli, P., Curatolo, P. "Autism: evidence of association with adenosine deaminase genetic polymorphism." *Neurogenetics* 2001 Mar;3(2):111-3.

Department of Internal Medicine, Tor Vergata University of Rome, Rome, Italy.

Reduced adenosine deaminase (ADA) activity has been reported in sera of autistic children relative to controls. Additionally, the Asn allele of the ADA Asp8Asn polymorphism has been associated with reduced enzymatic activity. Therefore, we studied this polymorphism in autistic children and controls from two Italian populations. We observed a significantly elevated frequency of the low-activity Asn allele in the total sample of autistic cases relative to controls ($P < 0.00001$), and in both study populations ($P < 0.001$ and $P < 0.025$). We suggest that this putative genotype-dependent reduction in ADA activity may be a risk factor for the development of autism.

1.3.117. Wolpert, C.M., Donnelly, S.L., Cuccaro, M.L., Hedges, D.J., Poole, C.P., Wright, H.H., Gilbert, J.R., Pericak-Vance, M.A. "De novo partial duplication of chromosome 7p in a male with autistic disorder." *Am J Med Genet* 2001 Apr 8;105(3):222-5.

Center for Human Genetics, Duke University Medical Center, Durham, North Carolina 27710, USA.

We describe a de novo partial duplication of 7p in a 25-year-old male with autistic disorder (AD). High-resolution chromosome analysis revealed an extra segment added to the proximal short arm of chromosome 7. The G-band pattern was consistent with an inverted duplication of 7p11.2-p14.1. Fluorescent in situ hybridization (FISH), using a whole chromosome 7 DNA probe (Cytocell, Inc., UK), confirmed that the extra chromosome material is derived from chromosome 7, indicating that the patient is partially trisomic for a region of the short arm of chromosome 7. Partial duplication of the short arm of chromosome 7 is uncommon with little more than 30 cases in the literature. This is the first report of an individual with a 7p duplication who also has AD. Copyright 2001 Wiley-Liss, Inc.

1.3.118. Herzog, L.B., Kim, S.J., Cook, E.H. Jr, Ledbetter, D.H. "The human aminophospholipid-transporting ATPase gene ATP10C maps adjacent to UBE3A and exhibits similar imprinted expression." *Am J Hum Genet* 2001 Jun;68(6):1501-5.

Department of Human Genetics, The University of Chicago, Chicago, IL 60637, USA.

Maternal duplications of the imprinted 15q11-13 domain result in an estimated 1%-2% of autism-spectrum disorders, and linkage to autism has been identified within 15q12-13. UBE3A, the Angelman syndrome gene, has, to date, been the only maternally expressed, imprinted gene identified within this region, but mutations have not been found in autistic patients. Here we describe the characterization of ATP10C, a new human imprinted gene, which encodes a putative protein homologous to the mouse aminophospholipid-transporting ATPase Atp10c. ATP10C maps within 200 kb distal to UBE3A and, like UBE3A, also demonstrates imprinted, preferential maternal expression in human brain. The location and imprinted expression of ATP10C thus make it a candidate for chromosome 15-associated autism and suggest that it may contribute to the Angelman syndrome phenotype.

1.3.119. Buxbaum, J.D., Silverman, J.M., Smith, C.J., Kilifarski, M., Reichert, J., Hollander, E., Lawlor, B.A., Fitzgerald, M., Greenberg, D.A., Davis, K.L. "Evidence for a susceptibility gene for autism on chromosome 2 and for genetic heterogeneity." *Am J Hum Genet* 2001 Jun;68(6):1514-20.

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Although there is considerable evidence for a strong genetic component to idiopathic autism, several genomewide screens for susceptibility genes have been performed with limited

concordance of linked loci, reflecting either numerous genes of weak effect and/or sample heterogeneity. Because decreasing sample heterogeneity would increase the power to identify genes, the effect on evidence for linkage of restricting a sample of autism-affected relative pairs to those with delayed onset (at age >36 mo) of phrase speech (PSD, for phrase speech delay) was studied. In the second stage of a two-stage genome screen for susceptibility loci involving 95 families with two or more individuals with autism or related disorders, a maximal multipoint heterogeneity LOD score (HLOD) of 1.96 and a maximal multipoint nonparametric linkage (NPL) score of 2.39 was seen on chromosome 2q. Restricting the analysis to the subset of families (n=49) with two or more individuals having a narrow diagnosis of autism and PSD generated a maximal multipoint HLOD score of 2.99 and an NPL score of 3.32. The increased scores in the restricted sample, together with evidence for heterogeneity in the entire sample, indicate that the restricted sample comprises a population that is more genetically homogeneous, which could therefore increase the likelihood of positional cloning of susceptibility loci.

1.3.120. Cook, E.H. Jr. "Genetics of autism." *Child Adolesc Psychiatr Clin N Am* 2001 Apr;10(2):333-50. Publication Types: Review, Review, Tutorial.

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In summary, autism genetics has moved from a time of identification of heritability and determination of risk of "lesser variants" or the "broader phenotype" in relatives to a phase where some cases of autism have a definite basis such as maternally inherited duplications of 15q11-q13, identification of mutations causing AS, Rett syndrome, and FRAXA. The first phase of genome-wide screens has not revealed definitive linkage, but as samples are enlarged and meta-analyses performed, the strongest linkage findings are likely to yield susceptibility variants once fine mapping proceeds. Recent statistical and molecular genetic analysis methods make the additional work feasible. However, frustrating it may be to be in this phase of the research, it is an essential part of the process of moving from identification of heritability in autism to understanding of the disorder in a way that may permit improved treatment in the future. If there is an advantage to autism being a complex rather than monogenic disorder, it is that the nature of multiplicative or interacting genetic risk is that prevention or treatment directed to any of the identified genetic risks may be sufficient to break a chain of pathophysiology. More genes increase the chance that one or more will have implications for treatment development sooner.

1.3.121. Williams, C.A., Lossie, A., Driscoll, D. "Angelman syndrome: mimicking conditions and phenotypes." *R.C. Phillips Unit. Am J Med Genet* 2001 Jun 1;101(1):59-64. Publication Types: Review, Review, Tutorial.

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The diagnosis of Angelman syndrome (AS) can be confirmed by genetic laboratory in about 80% of cases. In 20%, the diagnosis remains clinical, but often there is uncertainty about the correctness of the clinical diagnosis and alternative diagnoses may be investigated. In evaluating individuals for AS in our center since 1989, we have encountered several mimicking conditions, and additional ones have been reported in the literature. Mimicking conditions can be grouped into the areas of chromosome, single gene, and symptom complex anomalies. Microdeletions or microduplications include chromosome regions 2,4,17, 22, and 15. Single gene conditions include methylene tetrahydrofolate reductase deficiency (MTHFR), Rett syndrome, alpha-thalassemia retardation syndrome (ATR-X), and Gurrieri syndrome. Symptom complexes include cerebral palsy, static encephalopathy, Lennox-Gastaut syndrome, autism spectrum disorder, pervasive developmental delay (PDD), and mitochondrial disorders. We present a review of these mimicking disorders to increase the awareness about conditions that can lead to an incorrect clinical diagnosis of AS. Copyright 2001 Wiley-Liss, Inc.

1.3.122. Niklasson, L., Rasmussen, P., Oskarsdottir, S., Gillberg, C. "Neuropsychiatric disorders in the 22q11 deletion syndrome." *Genet Med* 2001 Jan-Feb;3(1):79-84.

Department of Child and Adolescent Psychiatry, University of Goteborg, Queen Silvia Children's Hospital, Sweden.

PURPOSE: This study was undertaken with a view to establishing the occurrence of neuropsychiatric disorders in the 22q11 deletion syndrome. METHODS: Thirty-two children and young adults with genetically confirmed 22q11 deletion were given comprehensive neuropsychiatric assessments. RESULTS: Altogether, 56% had a neuropsychiatric disorder. Only 6% were of normal IQ and free of psychiatric disorder. Attention-deficit/hyperactivity disorder was diagnosed in 44% and 31% had an autism spectrum problem. In 16% criteria for both these diagnoses were met. Fifty-three percent had mental retardation, often with a test-profile suggesting a nonverbal learning disorder. CONCLUSION: The findings imply that a majority of children and adolescents with 22q11 deletion syndrome are in need of neuropsychiatric assessment and intervention.

1.3.123. Persico, A.M., D'Agruma, L., Maiorano, N., Totaro, A., Militerni, R., Bravaccio, C., Wassink, T.H., Schneider, C., Melmed, R., Trillo, S., Montecchi, F., Palermo, M., Pascucci, T., Puglisi-Allegra, S., Reichelt, K.L., Conciatori, M., Marino, R., Quattrocchi, C.C., Baldi, A., Zelante, L., Gasparini, P., Keller, F. "Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder." *Collaborative Linkage Study of Autism. Mol Psychiatry* 2001 Mar;6(2):150-9.

Laboratory of Neuroscience, Department of Physiology and Neuroscience, Libera Universita Campus Bio-Medico, Via Longoni 83, I-00155 Rome, Italy.

Autistic disorder (MIM 209850) is currently viewed as a neurodevelopmental disease. Reelin plays a pivotal role in the development of laminar structures including the cerebral

cortex, hippocampus, cerebellum and of several brainstem nuclei. Neuroanatomical evidence is consistent with Reelin involvement in autistic disorder. In this study, we describe several polymorphisms identified using RNA-SSCP and DNA sequencing. Association and linkage were assessed comparing 95 Italian patients to 186 ethnically-matched controls, and using the transmission/disequilibrium test and haplotype-based haplotype relative risk in 172 complete trios from 165 families collected in Italy and in the USA. Both case-control and family-based analyses yield a significant association between autistic disorder and a polymorphic GGC repeat located immediately 5' of the reelin gene (RELN) ATG initiator codon, as well as with specific haplotypes formed by this polymorphism with two single-base substitutions located in a splice junction in exon 6 and within exon 50. Triplet repeats located in 5' untranslated regions (5'UTRs) are indicative of strong transcriptional regulation. Our findings suggest that longer triplet repeats in the 5'UTR of the RELN gene confer vulnerability to autistic disorder.

1.3.124. Borgatti, R., Piccinelli, P., Passoni, D., Dalpra, L., Miozzo, M., Micheli, R., Gagliardi, C., Balottin, U. "Relationship between clinical and genetic features in inverted duplicated chromosome 15" patients." *Pediatr Neurol* 2001 Feb;24(2):111-6.

Department of Child Neurorehabilitation, Scientific Institute "Eugenio Medea," Bosisio Parini (Lecco), Italy.

Inverted duplicated chromosome 15 (Inv dup [15]) syndrome is a genetic disorder characterized by psychologic or intellectual language delay; neurologic signs, such as hypotonia, ataxia, and epilepsy; mental retardation ranging from mild to severe; and facial dysmorphisms. All patients present with a psychopathologic impairment that is highly variable in severity but always classifiable as pervasive developmental disorder (PDD). Many genetic mechanisms have been hypothesized to explain the clinical variability. This article describes the neurologic and psychopathologic features of six Inv dup(15) patients, one male and five females, between 8 and 14 years of age, all with a maternal marker chromosome. Four patients were diagnosed with PDD not otherwise specified, whereas two patients received a diagnosis of autism. Epilepsy was present in three patients (two generalized symptomatic and one focal symptomatic), and a correlation between the severity of the disease and its outcome was not always observed. Nevertheless, the influence of gene content of the marker chromosome, particularly the three gamma-aminobutyric acid-A receptor subunit genes, may represent the link between epilepsy, mental retardation, and PDD.

1.3.125. Shastry, B.S. "Molecular genetics of Rett syndrome." *Neurochem Int* 2001 May;38(6):503-8. Publication Types: Review, Review, Tutorial.

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Rett syndrome is a neurodevelopmental disorder affecting almost exclusively females. It affects approximately one in 15000 females and is characterized by a loss of purposeful

hand use, autism, ataxia and seizure. The disorder is usually sporadic, but rare familial cases have also been reported. Recently it has been shown that familial cases are an X-linked dominant disorder and the disease locus maps to Xq28. A candidate gene called methyl-CpG-binding protein 2 was identified from the Xq28 region and was shown to contain mutations in about 77% of Rett syndrome patients. Since the encoded protein was previously shown to be a global transcriptional repressor, undesired expression of yet unidentified genes that are normally repressed is considered to be pathogenic in Rett syndrome.

1.3.126. Taieb, O., Baleyte, J.M., Mazet, P., Fillet, A.M. "Borna disease virus and psychiatry." *Eur Psychiatry* 2001 Feb;16(1):3-10. Publication Types: Review, Review, Tutorial.

Department of Virology, CERVI, 47-83 Boulevard de l'Hopital, 75013 Paris, France.

Borna disease virus (BDV), a noncytolytic neurotropic nonsegmented negative-stranded RNA virus with a wide geographic distribution, infects several vertebrate animal species and causes an immune-mediated central nervous system (CNS) disease with various manifestations, depending on both host and viral factors. In animal infections, BDV can persist in the CNS and induce alterations in brain cell functions, neurodevelopmental abnormalities and behavioral disturbances. An association between BDV and psychiatric disorders (essentially schizophrenia and affective disorders) has been suggested by some serologic and molecular studies but further investigations are required to substantiate the possible contribution of this virus to the pathogenesis of these disorders.

1.3.127. Daniels, R.J., Peden, J.F., Lloyd, C., Horsley, S.W., Clark, K., Tufarelli, C., Kearney, L., Buckle, V.J., Doggett, N.A., Flint, J., Higgs, D.R. "Sequence, structure and pathology of the fully annotated terminal 2 Mb of the short arm of human chromosome 16." *Hum Mol Genet* 2001 Feb 15;10(4):339-52.

MRC Molecular Haematology Unit, Weatherall Institute for Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, UK.

We have sequenced 1949 kb from the terminal Giemsa light band of human chromosome 16p, enabling us to fully annotate the region extending from the telomeric repeats to the previously published tuberous sclerosis disease 2 (TSC2) and polycystic kidney disease 1 (PKD1) genes. This region can be subdivided into two GC-rich, Alu-rich domains and one GC-rich, Alu-poor domain. The entire region is extremely gene rich, containing 100 confirmed genes and 20 predicted genes. Many of the genes encode widely expressed proteins orchestrating basic cellular processes (e.g. DNA recombination, repair, transcription, RNA processing, signal transduction, intracellular signalling and mRNA translation). Others, such as the alpha globin genes (HBA1 and HBA2), PDIP and BAIAP3, are specialized tissue-restricted genes. Some of the genes have been previously implicated in the pathophysiology of important human genetic diseases (e.g. asthma, cataracts and the ATR-16 syndrome). Others are

known disease genes for alpha thalassaemia, adult polycystic kidney disease and tuberous sclerosis. There is also linkage evidence for bipolar affective disorder, epilepsy and autism in this region. Sixty-three chromosomal deletions reported here and elsewhere allow us to interpret the results of removing progressively larger numbers of genes from this well defined human telomeric region.

1.3.128. Sabaratnam, M., Turk, J., Vroegop, P. "Case report: autistic disorder and chromosomal abnormality 46, XX duplication (4) p12-p13." *Eur Child Adolesc Psychiatry* 2000 Dec;9(4):307-11.

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We report an 18-year-old female with a diagnosis of DSM-IV Autistic Disorder and moderate to severe mental retardation who was discovered to have a previously undescribed chromosomal abnormality 46, XX, duplication (4) p12-p13. We discuss her history and diagnosis, noting that the co-occurrence of her diagnoses have not previously been documented. The report adds to the literature supporting the argument that individuals with autistic spectrum disorders should be re-examined for chromosomal abnormalities.

1.3.129. Bardoni, B., Mandel, J.L., Fisch, G.S. "FMR1 gene and fragile X syndrome." *Am J Med Genet* 2000 Summer;97(2):153-63. Publication Types: Review, Review, Tutorial.

Institute of Medical Genetics at the Pavia Faculty of Medicine, Italy.

Taxonomic features of fragile X syndrome (FXS) associated with the fragile X mutation have evolved over several decades. Males are more severely impacted cognitively than females, but both show declines in IQ scores as they age. Although many males with FXS exhibit autistic-like features, autism does not occur more frequently in males with FXS than among males with mental retardation (MR). FXS is caused by inactivation of the FMR1 gene located on Xq27.3. FMRP, the protein produced by FMR1, has been detected in most organs and in brain. In cells, it is located primarily in cytoplasm and contains motifs found in RNA-binding proteins. The FMRP N-terminal contains a functional nuclear localization signal which permits the protein to shuttle between cytoplasm and nucleus. FMR1 knockout mice show subtle behavioral and visual-spatial difficulties. Analysis of their brain tissue suggests absence of FMRP impairs synaptic maturation. Individuals with the fragile premutation produce FMRP, and the phenotype associated with the premutation has been controversial. However, there seems to be a higher incidence of premature ovarian failure in women with the premutation than is found in the general female population. This may be related to unusual increases in mRNA levels in premutation carriers.

1.3.130. Ozonoff, S., Williams, B.J., Rauch, A.M., Opitz, J.O. "Behavior phenotype of FG syndrome: cognition, personality, and behavior in eleven affected boys." *Am J Med Genet* 2000 Summer;97(2):112-8.

Department of Psychology, University of Utah, Salt Lake City 84112-0251, USA. sally.ozonoff@hsc.utah.edu

In this study we examined several behavioral, personality, and cognitive characteristics of boys with FG syndrome. We confirmed high rates of attention and activity level problems, which were described previously. Nine of the 11 patients met criteria for attention deficit/hyperactivity disorder. The boys did not manifest autistic behavior, and none met criteria for an autism spectrum disorder, though their parents reported substantial repetitive behavior. The personalities of the participants often were described as friendly, good-natured, and cheerful, but they did not differ empirically on a standardized measure of personality structure from typically developing comparison children, even after controlling for the effects of IQ. Specifically, higher rates of agreeableness and extraversion were not confirmed, though these constructs do not correspond perfectly with the traits of affability and gregariousness described in earlier published case studies of FG syndrome. In terms of neuropsychological assessment, the boys had relatively less developed language, fine motor, and executive function skills, and visual-spatial abilities were a relative strength. Limitations and suggestions for future research are discussed.

1.3.131. Veenstra-VanderWeele, J., Anderson, G.M., Cook, E.H. Jr. "Pharmacogenetics and the serotonin system: initial studies and future directions." *Eur J Pharmacol* 2000 Dec 27;410(2-3):165-181. Publication Types: Review, Review, Academic.

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Serotonin (5-hydroxytryptamine, 5-HT) appears to play a role in the pathophysiology of a range of neuropsychiatric disorders, and serotonergic agents are of central importance in neuropharmacology. Genes encoding various components of the 5-HT system are being studied as risk factors in depression, schizophrenia, obsessive-compulsive disorder, aggression, alcoholism, and autism. Recently, pharmacogenetic research has begun to examine possible genetic influences on therapeutic response to drugs affecting the serotonin system. Genes regulating the synthesis (TPH), storage (VMAT2), membrane uptake (HTT), and metabolism (MAOA) of 5-HT, as well as a number of 5-HT receptors (HTR1A, HTR1B, HTR2A, HTR2C, and HTR5A), have been studied and this initial research is reviewed here. After a brief introduction to serotonin neurobiology and a general discussion of appropriate genetic methodology, each of the major 5-HT-related genes and their encoded proteins are reviewed in turn. For each gene, relevant polymorphisms and research on functional variants are discussed; following brief reviews of the disorder or trait association and linkage studies, pharmacogenetic studies performed to date are covered. The critical and manifold roles of the serotonin system, the great abundance of targets within the system, the wide range of serotonergic agents-available and in development-and the

promising preliminary results suggest that the serotonin system offers a particularly rich area for pharmacogenetic research.

1.3.132. Wassink, T.H., Piven, J. "The molecular genetics of autism." *Curr Psychiatry Rep* 2000 Apr;2(2):170-5. Publication Types: Review, Review, Tutorial.

Psychiatry Research, MEB, Department of Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA.

Autism is a severe neurodevelopmental disorder characterized by communication and social deficits and by stereotyped, repetitive behaviors. The syndrome of autism is highly heritable, is considered to be etiologically heterogeneous and is thought to be the result of multiple, interacting genes. It is more common than previously thought, and has a complex pattern of genetic transmission. From four recently completed genome-wide linkage screens of autism, distal 7q has emerged as the most prominent chromosomal region of interest. Additional support for 7q comes from autistic individuals with gross 7q cytologic abnormalities, and from linkage and association data in families with language and speech disorders. Chromosome 15q11-13 is also of interest because of numerous reports of macroscopic and molecular abnormalities in the region associated with Prader-Willi and Angelman syndromes. In this review, molecular aspects of these data, as well as future avenues of investigation, are discussed.

1.3.133. Goizet, C., Excoffier, E., Taine, L., Taupiac, E., El Moneim, A.A., Arveiler, B., Bouvard, M., Lacombe, D. "Case with autistic syndrome and chromosome 22q13.3 deletion detected by FISH." *Am J Med Genet* 2000 Dec 4;96(6):839-44. Publication Types: Review, Review of Reported Cases.

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Autism is a rare neurodevelopmental disorder with a strong genetic component. Co-occurrence of autism and chromosomal abnormalities is useful to localize candidate regions that may include gene(s) implicated in autism determinism. Several candidate chromosomal regions are known, but association of chromosome 22 abnormalities with autism is unusual. We report a child with autistic syndrome and a de novo 22q13.3 cryptic deletion detected by FISH. Previously described cases with 22q13.3 deletions shared characteristic developmental and speech delay, but autism was not specifically reported. This case emphasizes a new candidate region that may bear a gene involved in autism etiopathogenesis. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:839-844, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.134. Persico, A.M., Militerni, R., Bravaccio, C., Schneider, C., Melmed, R., Trillo, S., Montecchi, F., Palermo, M.T., Pascucci, T., Puglisi-Allegra, S., Reichelt, K.I., Conciatori, M., Baldi, A., Keller, F. "Adenosine deaminase alleles and autistic disorder: case-control and family-based association studies." *Am J Med Genet* 2000 Dec 4;96(6):784-90.

Laboratory of Neuroscience, Department of Physiology and Neuroscience, Libera Università Campus Bio-Medico, Rome, Italy.

Adenosine deaminase (ADA) plays a relevant role in purine metabolism, immune responses, and peptidase activity, which may be altered in some autistic patients. Codominant ADA1 and ADA2 alleles code for ADA1 and ADA2 allozymes, the most frequent protein isoforms in the general population. Individuals carrying one copy of the ADA2 allele display 15 to 20% lower catalytic activity compared to ADA1 homozygotes. Recent preliminary data suggest that ADA2 alleles may be more frequent among autistic patients than healthy controls. The present study was undertaken to replicate these findings in a new case-control study, to test for linkage/association using a family-based design, and to characterize ADA2-carrying patients by serotonin blood levels, peptiduria, and head circumference. ADA2 alleles were significantly more frequent in 91 Caucasian autistic patients of Italian descent than in 152 unaffected controls (17.6% vs. 7.9%, $P = 0.018$), as well as among their fathers. Family-based tests involving these 91 singleton families, as well as 44 additional Caucasian-American trios, did not support significant linkage/association. However, the observed preferential maternal transmission of ADA2 alleles, if replicated, may point toward linkage disequilibrium between the ADA2 polymorphism and an imprinted gene variant located in its vicinity. Racial and ethnic differences in ADA allelic distributions, together with the low frequency of the ADA2 allele, may pose methodological problems to future linkage/association studies. Direct assessments of ADA catalytic activity in autistic individuals and unaffected siblings carrying ADA1/ADA1 vs ADA1/ADA2 genotypes may provide stronger evidence of ADA2 contributions to autistic disorder. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:784-790, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.135. Smith, M., Filipek, P.A., Wu, C., Bocian, M., Hakim, S., Modahl, C., Spence, M.A. "Analysis of a 1-megabase deletion in 15q22-q23 in an autistic patient: identification of candidate genes for autism and of homologous DNA segments in 15q22-q23 and 15q11-q13." *Am J Med Genet* 2000 Dec 4;96(6):765-70.

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We have identified a one megabase deletion in the 15q22-15q23 region in a patient with autism, developmental delay, and mild dysmorphism. Genes that map within the deletion region and genes that are interrupted or rearranged at the deletion breakpoints are candidate genes for autism. Fluorescence in situ hybridization studies in this patient revealed that part or all of the PML gene is absent from one chromosome 15 and a BAC clone containing the D15S124 gene locus hybridizes to only one chromosome 15. BAC clones containing the PTPN9, and SLP-1[hUNC24] genes showed markedly reduced hybridization in the 15q22-q23 region on one chromosome 15 in the patient. These BACs also hybridize to the 15q11-q13 region in close proximity to SNRPN and HERC2, and in this

region there is equal intensity of signal on the normal and on the deleted chromosome. There are previous reports of deletions and duplications of the 15q11-q13 region in patients with autism. Our patient represents the first report of a 15q22-q23 deletion. Hybridization of the PTPN9 and Slp-1 Bac clones to the 15q11-q13 and the 15q22-q23 regions of chromosome 15 may be due to the presence of PTPN9 or SLP-1 gene sequences or to the presence of other gene sequences or to non-coding homologous DNA sequences. The PTPN9 gene encodes a non-receptor protein tyrosine phosphatase. The Slp-1 [hUNC24] gene is expressed mainly in the brain. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:765-770, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.136. Yan, W.L., Guan, X.Y., Green, E.D., Nicolson, R., Yap, T.K., Zhang, J., Jacobsen, L.K., Krasnewich, D.M., Kumra, S., Lenane, M.C., Gochman, P., Damschroder-Williams, P.J., Esterling, L.E., Long, R.T., Martin, B.M., Sidransky, E., Rapoport, J.L., Ginns, F.I. "Childhood-onset schizophrenia/autistic disorder and t(1;7) reciprocal translocation: identification of a BAC contig spanning the translocation breakpoint at 7q21." *Am J Med Genet* 2000 Dec 4;96(6):749-53.

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Childhood-onset schizophrenia (COS) is defined by the development of first psychotic symptoms by age 12. While recruiting patients with COS refractory to conventional treatments for a trial of atypical antipsychotic drugs, we discovered a unique case who has a familial t(1;7)(p22;q21) reciprocal translocation and onset of psychosis at age 9. The patient also has symptoms of autistic disorder, which are usually transient before the first psychotic episode among 40-50% of the childhood schizophrenics but has persisted in him even after the remission of psychosis. Cosegregating with the translocation, among the carriers in the family available for the study, are other significant psychopathologies, including alcohol/drug abuse, severe impulsivity, and paranoid personality and language delay. This case may provide a model for understanding the genetic basis of schizophrenia or autism. Here we report the progress toward characterization of genomic organization across the translocation breakpoint at 7q21. The polymorphic markers, D7S630/D7S492 and D7S2410/D7S646, immediately flanking the breakpoint, may be useful for further confirming the genetic linkage for schizophrenia or autism in this region. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:749-753, 2000. Published 2000 Wiley-Liss, Inc.

1.3.137. Constantino, J.N., Todd, R.D. "Genetic structure of reciprocal social behavior." *Am J Psychiatry* 2000 Dec;157(12):2043-5. Publication Types: Twin Study.

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OBJECTIVE: The study examined the genetic structure of deficits in reciprocal social behavior in an epidemiologic sample of male twins. **METHOD:** Parents of 232 pairs of 7-

15-year-old male twins completed the Social Reciprocity Scale to provide data on their children's reciprocal social behavior. Scale scores were analyzed by using structural equation modeling. **RESULTS:** Intraclass (twin-twin) correlations for scores on the Social Reciprocity Scale were 0.73 for monozygotic twins (N=98 pairs) and 0.37 for dizygotic twins (N=134 pairs). The best fitting model of causal influences on reciprocal social behavior incorporated additive genetic influences and unique environmental influences. **CONCLUSIONS:** For school-age boys in the general population, reciprocal social behavior is highly heritable, with a genetic structure similar to that reported for autism in clinical samples. Continuous measures of reciprocal social behavior may be useful for characterizing the broader autism phenotype and may enhance the statistical power of genetic studies of autism.

1.3.138. Murphy, M., Bolton, P.F., Pickles, A., Fombonne, E., Piven, J., Rutter, M. "Personality traits of the relatives of autistic probands." *Psychol Med* 2000 Nov;30(6):1411-24.

MRC Child Psychiatry Unit and Social, Genetic and Development Psychiatry Research Centre, Institute of Psychiatry, London.

BACKGROUND: There is substantial evidence that the genetic liability to autism confers a risk for a range of more subtle social and communication impairments, as well as stereotyped and repetitive behaviours. Recent research suggests that increased expression of particular personality traits may be a manifestation of the liability to autism. **METHODS:** To investigate this we examined the personality traits of the adult relatives of 99 autistic and 36 Down's syndrome probands, using the informant version of the Modified Personality Assessment Schedule. **RESULTS:** There was significantly increased expression of the traits anxious, impulsive, aloof, shy, over-sensitive, irritable and eccentric among the autism relatives with evidence of different profiles for male and female relatives and for parents and adult children. Factor analysis revealed three broad groups of traits, two of which ('withdrawn' and 'difficult') appeared to reflect impairments in social functioning and a third group of anxiety related traits ('tense'). Each of these factors differed in their pattern of associations with the factor we termed 'withdrawn' showing a similar pattern of association to that found for other autism related conditions. The 'tense' factor appeared in part to be related to the burden of caring for an autistic child. **CONCLUSIONS:** This study confirms the finding that particular personality traits may aggregate in the family members of autistic individuals and furthermore that some of these traits may be a manifestation of the liability to autism.

1.3.139. Ingram, J.L., Stodgell, C.J., Hyman, S.L., Figlewicz, D.A., Weitkamp, L.R., Rodier, P.M. "Discovery of allelic variants of HOXA1 and HOXB1: genetic susceptibility to autism spectrum disorders." *Teratology* 2000 Dec;62(6):393-405.

Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, USA.

BACKGROUND: Family studies have demonstrated that the autism spectrum disorders (ASDs) have a major genetic etiologic component, but expression and penetrance of the phenotype are variable. Mice with null mutations of *Hoxa1* or *Hoxb1*, two genes critical to hindbrain development, have phenotypic features frequently observed in autism, but no naturally occurring variants of either gene have been identified in mammals. **METHODS:** By sequencing regions of genomic DNA of patients with autism spectrum disorders, we detected a substitution variant at *HOXA1* and an insertion variant at *HOXB1*, both in coding regions of the genes. Fifty-seven individuals ascertained for a diagnosis of an ASD, along with 166 of their relatives, were typed for these variants. Two non-ASD populations were typed, and the frequency of the newly identified alleles was determined in all groups. The genotypes of the ASD families were tested for conformation to Hardy-Weinberg proportions and Mendelian expectations for gene transmission. **RESULTS:** The frequency of the variants was 10-25% in persons of European or African origin. In the ASD families, there was a significant deviation from the *HOXA1* genotype ratios expected from Hardy-Weinberg proportions ($P = 0.005$). Among affected offspring, a significant deviation from Mendelian expectation in gene transmission ($P = 0.011$) was observed. No statistically significant effects were detected when the same analyses were applied to the *HOXB1* locus, but there was evidence of an interaction between *HOXA1*, *HOXB1*, and gender in susceptibility to ASDs. **CONCLUSIONS:** The results support a role for *HOXA1* in susceptibility to autism, and add to the existing body of evidence implicating early brain stem injury in the etiology of ASDs. Copyright 2000 Wiley-Liss, Inc.

1.3.140. Michaelis, R.C., Copeland-Yates, S.A., Sossey-Alaoui, K., Skinner, C., Friez, M.J., Longshore, J.W., Simensen, R.J., Schroer, R.J., Stevenson, R.E. "The HOPA gene dodecamer duplication is not a significant etiological factor in autism." *J Autism Dev Disord* 2000 Aug;30(4):355-8.

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A recent study has suggested that a dodecamer duplication in the HOPA gene in Xq13 may occur in a significant portion of male patients with autism. We have determined the incidence of this duplication in 202 patients from the South Carolina Autism Study. The incidence of the duplication was not significantly different between patients and controls. Three of the female patients inherited the duplication from nonautistic fathers. In addition, there was no systematic skewing of X inactivation in the female patients with the duplication, or in nonautistic mothers and sisters with the duplication. These findings suggest that the dodecamer duplication in the HOPA gene does not play a significant role in the etiology of autism.

1.3.141. Orrico, A., Lam, C., Galli, L., Dotti, M.T., Hayek, G., Tong, S.F., Poon, P.M., Zappella, M., Federico, A., Sorrentino, V. "MECP2 mutation in male patients with non-specific X-linked mental retardation." *FEBS Lett* 2000 Sep 22;481(3):285-8.

Medical Genetics, Policlinico Le Scotte, Sienna, Italy.

In contrast to the preponderance of affected males in families with X-linked mental retardation, Rett syndrome (RTT) is a neurological disorder occurring almost exclusively in females. The near complete absence of affected males in RTT families has been explained by the lethal effect of an X-linked gene mutation in hemizygous affected males. We report here on a novel mutation (A140V) in the *MECP2* gene detected in one female with mild mental retardation. In a family study, the A140V mutation was found to segregate in the affected daughter and in four adult sons with severe mental retardation. These results indicate that *MECP2* mutations are not necessarily lethal in males and that they can be causative of non-specific X-linked mental retardation.

1.3.142. Mouridsen, S.E., Rich, B., Isager, T. "A comparative study of genetic and neurobiological findings in disintegrative psychosis and infantile autism." *Psychiatry Clin Neurosci* 2000 Aug;54(4):441-6.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

Although disintegrative psychosis (DP) was first described in 1908, the validity of the syndrome has not yet been fully documented. To investigate the validity of DP as defined in ICD-9, 13 cases of DP were compared with 39 cases of infantile autism with reference to lifetime parental psychopathology, neuroradiological findings and genetic abnormalities. The groups were matched for gender, age, intellectual level and social class. Apart from a significantly higher rate of electroencephalogram abnormalities in the disintegrative group there was very little in the neurobiological background to support a clear distinction between DP and infantile autism.

1.3.143. Bass, M.P., Menold, M.M., Wolpert, C.M., Donnelly, S.L., Ravan, S.A., Hauser, E.R., Maddox, L.O., Vance, J.M., Abramson, R.K., Wright, H.H., Gilbert, J.R., Cuccaro, M.L., DeLong, G.R., Pericak-Vance, M.A. "Genetic studies in autistic disorder and chromosome 15." *Neurogenetics* 2000 Mar;2(4):219-26.

Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA.

Autistic disorder (AD) is a developmental disorder affecting social interactions, communication, and behavior. AD is a disease of complex genetic architecture. It is postulated that several genes contribute to the underlying etiology of AD. Chromosome 15 is of particular interest due to numerous reports of AD in the presence of chromosomal abnormalities, located mainly in the 15q11-q13 region. There are also a number of plausible candidate genes in this area, including the gamma-aminobutyric acid A (GABA(A)) receptor gene complex. We have undertaken a study of this region of chromosome 15 in a data set of 63 multiplex families (with 2 or more AD affected individuals per family). We found evidence in support of linkage to the 15q11-q13 region, as well as evidence of increased recombination in this region. These findings provide further support for the involvement of chromosome 15q11-q13 in the genetic etiology of AD.

1.3.144. Kelley, R.I. "Inborn errors of cholesterol biosynthesis." *Adv Pediatr* 2000;47:1-53. Publication Types: Review, Review, Tutorial.

Johns Hopkins University, Baltimore, Md., USA.

Disorders of cholesterol biosynthesis have recently emerged as important errors of metabolism that collectively have taught us many new genetic and biochemical lessons. Whereas most metabolic diseases are characterized by exclusively or largely postnatal biochemical toxicities or deficiencies, disorders of cholesterol biosynthesis are notable for their severe effects on prenatal development. The remarkable embryonic consequences of abnormal cholesterol biosynthesis are exemplified by Smith-Lemli-Opitz syndrome (SLOS), a well-known multiple congenital anomaly syndrome only recently discovered to be caused by a deficiency in the last step in cholesterol biosynthesis. Equally surprising has been the discovery that primary defects of cholesterol biosynthesis cause several different forms of congenital skeletal dysplasia, most notably X-linked dominant chondrodysplasia punctata, or Conradi-Hunermann syndrome. Yet another sterol disorder, desmosterolosis, caused by defective activity of desmosterol reductase, combines a severe osteosclerotic skeletal dysplasia with multiple embryonic malformations similar to those of SLOS. The discovery of the biochemical basis of these diverse genetic disorders has provided not only accurate biochemical methods for their diagnosis and prenatal diagnosis, but also new insights into the biochemistry of vertebrate embryonic development. Among the lessons we have learned from the study of inborn errors of cholesterol biosynthesis, one of the most important is that the abnormal cholesterol metabolism of SLOS impairs the function of "Sonic hedgehog" and other related embryonic "signaling proteins" that help determine the vertebrate body plan during the earliest weeks of embryonic development. Most significant clinically has been the realization that many of the postnatal clinical problems of patients with SLOS are direct consequences of the inability to synthesize the large amounts of cholesterol needed for growth and for the synthesis of compounds derived from cholesterol, such as steroid hormones. In addition to the important finding that supplementary cholesterol eliminates or ameliorates many of the feeding and growth problems of SLOS, the discovery that the autistic behaviors of children with SLOS can be reduced or even eliminated by treatment with supplementary dietary cholesterol has been one of the most startling. Moreover, clinical and basic research on prenatal cholesterol nutrition in SLOS and various animal model systems has delineated a previously unrecognized system for the delivery of low-density lipoprotein cholesterol from the mother to the developing embryo. The many discoveries engendered by these experiments of nature argue that there are heretofore unrecognized beneficial effects of cholesterol, especially in children, and that we should consider very carefully possible adverse effects that the popular war against cholesterol may have on the prenatal and postnatal development of children.

1.3.145. Jones, W., Bellugi, U., Lai, Z., Chiles, M., Reilly, J., Lincoln, A., Adolphs, R. "II. Hypersociability in Williams Syndrome." *J Cogn Neurosci* 2000;12 Suppl 1:30-46.

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Studies of abnormal populations provide a rare opportunity for examining relationships between cognition, genotype and brain neurobiology, permitting comparisons across these different levels of analysis. In our studies, we investigate individuals with a rare, genetically based disorder called Williams syndrome (WMS) to draw links among these levels. A critical component of such a cross-domain undertaking is the clear delineation of the phenotype of the disorder in question. Of special interest in this paper is a relatively unexplored unusual social phenotype in WMS that includes an overfriendly and engaging personality. Four studies measuring distinct aspects of hypersocial behavior in WMS are presented, each probing specific aspects in WMS infants, toddlers, school age children, and adults. The abnormal profile of excessively social behavior represents an important component of the phenotype that may distinguish WMS from other developmental disorders. Furthermore, the studies show that the profile is observed across a wide range of ages, and emerges consistently across multiple experimental paradigms. These studies of hypersocial behavior in WMS promise to provide the groundwork for crossdisciplinary analyses of gene-brain-behavior relationships.

1.3.146. Szatmari, P., MacLean, J.E., Jones, M.B., Bryson, S.E., Zwaigenbaum, L., Bartolucci, G., Mahoney, W.J., Tuff, L. "The familial aggregation of the lesser variant in biological and nonbiological relatives of PDD probands: a family history study." *J Child Psychol Psychiatry* 2000 Jul;41(5):579-86

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OBJECTIVE: To determine the risk of the lesser variant (or PDD-like traits) in the biological and nonbiological second- and third-degree relatives of PDD probands using a screening questionnaire and to investigate the extent to which the risk of the lesser variant differs according to various characteristics of the proband. **METHOD:** The sample consists of a series of 34 nuclear families with 2 affected PDD children (multiplex, MPX), 44 families with a single PDD child (simplex, SPX), and 14 families who adopted a PDD child. Data on characteristics of the lesser variant in 1362 biological and 337 nonbiological second- and third-degree relatives were collected from parents by telephone interview and from several maternal and paternal relatives by questionnaire. **RESULTS:** All components of the lesser variant were more common in biological relatives (BR) than nonbiological relatives (NBR), confirming the familial aggregation of the traits. Proband characteristics associated with an increased risk of the lesser variant in relatives were a higher level of functioning and coming from a MPX family. **CONCLUSIONS:** These findings on the familial aggregation of the lesser variant suggest that the genes for PDD also confer susceptibility to the lesser variant and that PDD may be a genetically heterogeneous disorder.

1.3.147. Hoh, J., Ott, J. "Scan statistics to scan markers for susceptibility genes." *Proc Natl Acad Sci U S A* 2000 Aug 15;97(17):9615-7.

Laboratory of Statistical Genetics, Rockefeller University, New York, NY 10021, USA.

Scan statistics are applied to combine information on multiple contiguous genetic markers used in a genome screen for susceptibility loci. This information may be, for example, allele sharing proportions for sib pairs or logarithm of odds (lod) scores in general small families. We focus on a dichotomous outcome variable, for example, case and control individuals or affected-affected versus affected-unaffected siblings, and suitable single-marker statistics. A significant scan statistic based on the single-marker statistics represents evidence of the presence of a susceptibility gene. For a given length of the scan statistic, we assess its significance by Monte Carlo permutation tests. Comparing P values for varying lengths of scan statistics, we treat the smallest observed P value as our statistic of interest and determine its overall significance level. We applied this method to a genome screen with autism families. The result was informative and surprising: A susceptibility region was found (genome-wide significance level, $P = 0.038$), which is missed with conventional approaches.

1.3.148. Tierney, E., Nwokoro, N.A., Kelley, R.I. "Behavioral phenotype of RSH/Smith-Lemli-Opitz syndrome." *Ment Retard Dev Disabil Res Rev* 2000;6(2):131-4. Publication Types: Review, Review, Tutorial.

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Smith-Lemli-Opitz syndrome (SLOS, RSH/SLO syndrome, MIM 270400) is an autosomal recessive multiple malformation/mental retardation syndrome initially described by Smith et al. [1964] that is due to a defect in cholesterol biosynthesis. The behavioral phenotype of Smith-Lemli-Opitz syndrome demonstrates cognitive abilities from borderline intellectual functioning to profound mental retardation, sensory hyperreactivity, irritability, language impairment, sleep cycle disturbance, self-injurious behavior, and autism spectrum behaviors. In a recent study of 28 subjects, 14 subjects (50%) with SLOS also exhibited the behavior of throwing themselves backward in a characteristic upper body movement ("opisthokinesis") and 2 adolescents had a stretching motion of the upper body accompanied by hand flicking [Tierney et al., 1999]. In that same study, 6 of 13 subjects (46%) met the Autism Diagnostic Interview-Revised (ADI-R) algorithm criteria (Lord et al. [1993] *Infant Mental Health* 14:234-252; Lord et al. [1994] *J Autism Dev Disord* 24:659-685) and the Diagnostic and Statistical Manual (APA [1994] DSM-IV) diagnostic criteria for autistic disorder. Smith-Lemli-Opitz syndrome is a metabolic disorder that is associated with autism. *MRDD Research Reviews* 2000;6:131-134. Copyright 2000 Wiley-Liss, Inc.

1.3.149. Wolpert, C.M., Menold, M.M., Bass, M.P., Qumsiyeh, M.B., Donnelly, S.L., Ravan, S.A., Vance, J.M., Gilbert, J.R., Abramson, R.K., Wright, H.H., Cuccaro, M.L., Pericak-Vance, M.A. "Three probands with autistic disorder and isodicentric chromosome 15." *Am J Med Genet* 2000 Jun 12;96(3):365-72. Publication Types: Review, Review of Reported Cases.

Department of Medicine and the Center for Human Genetics, Duke University Medical Center, Durham, NC 27710, USA.

We have identified three unrelated probands with autistic disorder (AD) and isodicentric chromosomes that encompass the proximal region of 15q11.2. All three probands met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [DSM-IV; American Psychiatric Association, 1994], and International Classification of Diseases (ICD-10) diagnostic criteria for AD, confirmed with the Autism Diagnostic Interview-Revised (ADI-R). Chromosome analysis revealed the following karyotypes: 47,XX,+idic(15)(q11.2), 47,XX,+idic(15)(q11.2), and 47,XY,+idic(15)(q11.2). Haplotype analysis of genotypic marker data in the probands and their parents showed that marker chromosomes in all three instances were of maternal origin. Comparison of the clinical findings of the three AD probands with case reports in the published literature ($N = 20$) reveals a clustering of physical and developmental features. Specifically, these three probands and the majority of reported probands in the literature exhibited hypotonia ($n = 13$), seizures ($n = 13$), and delayed gross motor development ($n = 13$). In addition, clustering of the following clinical signs was seen with respect to exhibited speech delay ($n = 13$), lack of social reciprocity ($n = 11$), and stereotyped behaviors ($n = 12$). Collectively, these data provide further evidence for the involvement of chromosome 15 in AD as well as present preliminary data suggesting a clustering of clinical features in AD probands with proximal 15q anomalies.

1.3.150. Donnelly, S.L., Wolpert, C.M., Menold, M.M., Bass, M.P., Gilbert, J.R., Cuccaro, M.L., Delong, G.R., Pericak-Vance, M.A. "Female with autistic disorder and monosomy X (Turner syndrome): parent-of-origin effect of the X chromosome." *Am J Med Genet* 2000 Jun 12;96(3):312-6.

Department of Medicine and Center for Human Genetics, Duke University Medical Center, Durham, NC 27710, USA.

We have ascertained and examined a patient with autistic disorder (AD) and monosomy X (Turner syndrome). The patient met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)/International Classification of Diseases (ICD-10) criteria for AD verified by the Autism Diagnostic Interview-Revised. The patient exhibited both social and verbal deficits and manifested the classical physical features associated with monosomy X. Skuse et al. [1997: *Nature* 387:705-708] reported three such cases of AD and monosomy X in their study of Turner syndrome and social cognition. They observed that monosomy X females with a maternally inherited X chromosome had reduced social cognition when compared with monosomy X females with a paternally inherited X chromosome. All three cases of AD and monosomy

X were maternally inherited. Based on their data, they suggested that there was a gene for social cognition on the X chromosome that is imprinted and not expressed when the X chromosome is of maternal origin. Thus, we conducted parent-of-origin studies in our AD/monosomy X patient by genotyping X chromosome markers in the patient and her family. We found that the patient's X chromosome was of maternal origin. These findings represent the fourth documented case of maternal inheritance of AD and monosomy X and provide further support for the hypothesis that parent-of-origin of the X chromosome influences social cognition.

1.3.151. Nasr, A., Roy, M. "Association of a balanced chromosomal translocation (4; 12)(q21.3; q15), affective disorder and autism." *J Intellect Disabil Res* 2000 Apr;44 (Pt 2):170-4.

Queen Elizabeth Psychiatric Hospital, Birmingham, UK.

This case report describes a set of monozygotic twins with severe intellectual disability, autism and affective disorder with a balanced translocation between chromosomes 4 and 12. Their mother, who carries the same balanced translocation, had severe postnatal depression. The association between autism affective disorder and these chromosome break points has not been reported previously. The implications are discussed.

1.3.152. Warburton, P., Baird, G., Chen, W., Morris, K., Jacobs, B.W., Hodgson, S., Docherty, Z. "Support for linkage of autism and specific language impairment to 7q31 from two chromosome rearrangements involving band 7q31." *Am J Med Genet* 2000 Apr 3;96(2):228-34.

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Childhood autism is characterised by impairments in communication and reciprocal social interaction together with restricted/stereotyped interests, which are evident before 3 years of age. Specific developmental disorders of speech and language (SDDSL) are characterised by impairment in the development of expressive and/or receptive language skills which is not associated with intellectual, sensory, physical, or neurological impairment. Family and twin studies indicate a substantial genetic component in the aetiology of both disorders. They also reveal increased rates of SDDSL in relatives of autistic individuals, suggesting that this phenotype can represent one manifestation of the genetic liability for autism. Modelling of the recurrence risk for autism and milder phenotypes, such as SDDSL, suggest that three or four epistatic loci may be aetiologically involved. A recently published linkage study of an exceptional family with an apparently dominantly inherited SDDSL implicated chromosome band 7q31 as the site of the putative susceptibility locus (SPCH1). This region of chromosome 7 also shows strong linkage in multiplex families with autism. We present two individuals (one has autism, the other SDDSL.)

with different, apparently balanced chromosome rearrangements involving a breakpoint at 7q31.3. Fluorescence in situ hybridisation was used to localise the breakpoints to an approximately 1 cM interval between CFTR and D7S643. Our findings may be of interest and relevance to the genetic aetiology of autism, and helpful in the search for susceptibility loci for SDDSL and autism. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:228-234, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.153. Auranen, M., Nieminen, T., Majuri, S., Vanhala, R., Peltonen, L., Jarvela, I. "Analysis of autism susceptibility gene loci on chromosomes 1p, 4p, 6q, 7q, 13q, 15q, 16p, 17q, 19q and 22q in Finnish multiplex families." *Mol Psychiatry* 2000 May;5(3):320-2.

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The role of genetic factors in the etiology of the autistic spectrum of disorders has clearly been demonstrated. Ten chromosomal regions, on chromosomes 1p, 4p, 6q, 7q, 13q, 15q, 16p, 17q, 19q and 22q have potentially been linked to autism.1-8 We have analyzed these chromosomal regions in a total of 17 multiplex families with autism originating from the isolated Finnish population by pairwise linkage analysis and sib-pair analysis. Mild evidence for putative contribution was found only with the 1p chromosomal region in the susceptibility to autism. Our data suggest that additional gene loci exist for autism which will be detectable in and even restricted to the isolated Finnish population.

1.3.154. Vincent, J.B., Herbrick, J.A., Gurling, H.M., Bolton, P.F., Roberts, W., Scherer, S.W. "Identification of a novel gene on chromosome 7q31 that is interrupted by a translocation breakpoint in an autistic individual." *Am J Hum Genet* 2000 Aug;67(2):510-4.

Department of Genetics, The Hospital for Sick Children, Toronto, ON, Canada.

The results of genetic linkage studies for autism have suggested that a susceptibility locus for the disease is located on the long arm of chromosome 7 (7q). An autistic individual carrying a translocation, t(7;13)(q31.3;q21), with the chromosome 7 breakpoint located in the region of 7q implicated by genetic studies was identified. A novel gene known as "RAY1" (or "FAM4A1") was found to be directly interrupted by the translocation breakpoint. The gene, which was found to be encoded by 16 exons with evidence of alternative splicing, spanned > or =220 kb of DNA at 7q31.3. Mutation screening of the entire coding region in a set of 27 unrelated autistic individuals failed to identify phenotype-specific variants, suggesting that coding region mutations are unlikely to be involved in the etiology of autism. Apparent homologues of RAY1 have also been identified in mouse, rat, pig, chicken, fruit fly, and nematode. The human and mouse genes share similar splicing patterns, and their predicted protein products are 98% identical.

1.3.155. Pesi, R., Micheli, V., Jacomelli, G., Peruzzi, L., Camici, M., Garcia-Gil, M., Allegrini, S., Tozzi, M.G. "Cytosolic 5'-nucleotidase hyperactivity in erythrocytes of Lesch-Nyhan syndrome patients." *Neuroreport* 2000 Jun 26;11(9):1827-31.

Dipartimento di Fisiologia e Biochimica, Università di Pisa, Italy.

Lesch-Nyhan syndrome is a metabolic-neurological syndrome caused by the X-linked deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). Metabolic consequences of HGPRT deficiency have been clarified, but the connection with the neurological manifestations is still unknown. Much effort has been directed to finding other alterations in purine nucleotides in different cells of Lesch-Nyhan patients. A peculiar finding was the measure of appreciable amount of Z-nucleotides in red cells. We found significantly higher IMP-GMP-specific 5'-nucleotidase activity in the erythrocytes of seven patients with Lesch-Nyhan syndrome than in healthy controls. The same alteration was found in one individual with partial HGPRT deficiency displaying a severe neurological syndrome, and in two slightly hyperuricemic patients with a psychomotor delay. Since ZMP was a good substrate of 5'-nucleotidase producing Z-riboside, we incubated murine and human cultured neuronal cells with this nucleoside and found that it is toxic for our models, promoting apoptosis. This finding suggests an involvement of the toxicity of the Z-riboside in the pathogenesis of neurological disorders in Lesch-Nyhan syndrome and possibly in other pediatric neurological syndromes of uncertain origin.

1.3.156. Moore, S.J., Turnpenny, P., Quinn, A., Glover, S., Lloyd, D.J., Montgomery, T., Dean, J.C. "A clinical study of 57 children with fetal anticonvulsant syndromes." *J Med Genet* 2000 Jul;37(7):489-97.

Department of Medical Genetics, Medical School, Foresterhill, Aberdeen UK.

BACKGROUND: Anticonvulsants taken in pregnancy are associated with an increased risk of malformations and developmental delay in the children. To evaluate the pattern of abnormalities associated with prenatal anticonvulsant exposure further, we undertook a clinical study of 57 children with fetal anticonvulsant syndromes. **METHODS:** Fifty two children were ascertained through the Fetal Anticonvulsant Syndrome Association and five were referred to the Aberdeen Medical Genetics Service. Pregnancy and medical history were obtained through a standardised questionnaire and interview and the children were examined. **RESULTS:** Thirty four (60%) were exposed in utero to valproate alone, four (7%) to carbamazepine alone, four (7%) to phenytoin alone, and 15 (26%) to more than one anticonvulsant. Forty six (81%) reported behavioural problems, 22 (39%) with hyperactivity or poor concentration of whom four (7%) had a diagnosis of attention deficit and hyperactivity disorder. Thirty four (60%) reported two or more autistic features, of whom four had a diagnosis of autism and two of Asperger's syndrome. Forty four (77%) had learning difficulties, 46 (81%) had speech delay, 34 (60%) had gross motor delay, and 24 (42%) had fine motor

delay. Nineteen (33%) had glue ear and 40 (70%) had joint laxity involving all sizes of joints. Of 46 who had formal ophthalmic evaluation, 16 (34%) had myopia. **CONCLUSIONS:** Speech delay, joint laxity, glue ear, and myopia are common in the fetal anticonvulsant syndromes and autistic features and hyperactivity form part of the behavioural phenotype.

1.3.157. Graf, W.D., Marin-Garcia, J., Gao, H.G., Pizzo, S., Naviaux, R.K., Markusic, D., Barshop, B.A., Courchesne, E., Haas, R.H. "Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation." *J Child Neurol* 2000 Jun;15(6):357-61.

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We report a family with a heterogeneous group of neurologic disorders associated with the mitochondrial DNA G8363A transfer ribonucleic acid (RNA)_{Lys} mutation. The phenotype of one child in the family was consistent with autism. During his second year of life, he lost previously acquired language skills and developed marked hyperactivity with toe-walking, abnormal reciprocal social interaction, stereotyped mannerisms, restricted interests, self-injurious behavior, and seizures. Brain magnetic resonance imaging (MRI) and repeated serum lactate studies were normal. His older sister developed signs of Leigh syndrome with progressive ataxia, myoclonus, seizures, and cognitive regression. Her laboratory studies revealed increased MRI T2-weighted signal in the putamen and posterior medulla, elevated lactate in serum and cerebrospinal fluid, and absence of cytochrome c oxidase staining in muscle histochemistry. Molecular analysis in her revealed the G8363A mutation of the mitochondrial transfer RNA(Lys) gene in blood (82% mutant mitochondrial DNA) and muscle (86%). The proportions of mutant mitochondrial DNA from her brother with autism were lower (blood 60%, muscle 61%). It is likely that the origin of his autism phenotype is the pathogenic G8363A mitochondrial DNA mutation. This observation suggests that certain mitochondrial point mutations could be the basis for autism in some individuals.

1.3.158. Kim, S.J., Goner, D., Hanna, G.L., Leventhal, B.L., Cook, E.H. Jr. "Deletion polymorphism in the coding region of the human NESP55 alternative transcript of GNAS1." *Mol Cell Probes* 2000 Jun;14(3):191-4.

Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry MC3077, 5841 S. Maryland Avenue, Chicago, IL 60637, USA.

NESP55, a novel member of the chromogranins, was originally implicated as a precursor of a peptide LSAL with 5-HT_{1B} receptor antagonist activity. In humans, NESP55 (MIM 139320) is encoded by an alternative transcript of GNAS1, the gene encoding the guanine nucleotide-binding alpha subunit of G(S). As a result of the potential relevance of NESP55 to serotonergic neurotransmission, we screened its sequence using genomic DNA pools from autistic disorder, obsessive-compulsive disorder (OCD) probands and control subjects. Six single nucleotide polymorphisms (SNPs) were

identified and the allele frequencies of those SNPs were determined. In addition, a 24-bp in-frame deletion in the coding region was found in one of the OCD probands. To further investigate its pattern of inheritance and the relevance to studied phenotypes, we genotyped 123 total subjects from autism, OCD and attention deficit hyperactivity disorder (ADHD) families. The deletion was detected only in one OCD family and followed Mendelian inheritance. All subjects with the deletion were heterozygous. However, there are no specific behavioural or physical alterations in the subjects with this deletion variant. The physiological role of NESP55 in serotonergic neurotransmission as well as the effect of the deletion on its function should be evaluated in future studies. Copyright 2000 Academic Press.

1.3.159. Turner, M., Barnby, G., Bailey, A. **"Genetic clues to the biological basis of autism."** *Mol Med Today* 2000 Jun;6(6):238-44. Publication Types: Review, Review, Tutorial.

MRC Child Psychiatry Unit, Institute of Psychiatry, Denmark Hill, London, UK.

Autism, the prototypical pervasive developmental disorder, is characterized by impaired communication and social interaction, and by repetitive interests and behaviours. The core disorder probably affects around 5:10 000 individuals, of whom some three-quarters are male. Onset is in the first three years of life, and the disorder is associated with lifelong disabilities. Because of the clear evidence that idiopathic autism has a strong genetic basis, many groups are undertaking whole genome screens to identify susceptibility loci. We review the first results, and briefly consider the implications of molecular genetic findings for future research, diagnosis and management.

1.3.160. Pickles, A., Starr, E., Kazak, S., Bolton, P., Papanikolaou, K., Bailey, A., Goodman, R., Rutter, M. **"Variable expression of the autism broader phenotype: findings from extended pedigrees."** *J Child Psychol Psychiatry* 2000 May;41(4):491-502.

MRC Child Psychiatry Unit and the Institute of Psychiatry, King's College, London, UK. andrew.pickles@man.ac.uk

Factors influencing the rate, form, and severity of phenotypic expression among relatives of autistic probands are examined. Family history data on 3095 first- and second-degree relatives and cousins from 149 families with a child with autism and 36 families with a child with Down syndrome are studied. The results provide further evidence of an increased risk among autism relatives for the broadly defined autism phenotype. Of proband characteristics, severity of autism and obstetric optimality were confirmed as being related to familial loading for probands with speech. There was little variation in loading among probands lacking speech. The type of phenotypic profile reported in relatives appeared little influenced by characteristics of the relative or the proband, except for variation by degree of relative, parental status of relative, and perhaps proband's birth optimality score. Phenotypic rates among parents suggested reduced fitness for the severest and more communication-related forms of

expression but not for the more mild and social forms of expression. Patterns of expression within the families did not support a simple X-linked nor an imprinted X-linked mode of inheritance. The basis for sex differences in rates of expression is discussed.

1.3.161. Mas, C., Bourgeois, F., Bulfone, A., Levacher, B., Mugnier, C., Simonneau, M. **"Cloning and expression analysis of a novel gene, RP42, mapping to an autism susceptibility locus on 6q16."** *Genomics* 2000 Apr 1;65(1):70-4.

Neurogenetique, INSERM E9935, Hopital Robert Debre, 48 Boulevard Serurier, Paris, 75019, France.

We isolated a novel mouse gene, RP42, in a systematic search for genes expressed in proliferating neuroblasts whose human orthologs map to susceptibility loci for autism. This gene is intronless and encodes a putative 259-amino-acid protein that exhibits 30-36% overall sequence identity to a fission yeast and a nematode protein (GenPept Accession Nos. CAA17006 and CAB54261). Nevertheless, no homology to any known gene was found. RP42 has developmentally regulated expression, particularly in proliferating neuroblasts from which neocortical neurons originate. Its human ortholog is located in a cluster of embryonic neuronally expressed genes on the 6q16 chromosome, making it a positional candidate susceptibility gene for autism. Copyright 2000 Academic Press.

1.3.162. Rutter, M. **"Genetic studies of autism: from the 1970s into the millennium."** *J Abnorm Child Psychol* 2000 Feb;28(1):3-14. Publication Types: Review, Review, Tutorial.

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Reviewers in the 1960s and early 1970s were skeptical about any substantial role for genetic factors in the etiology of autism. A realization that the 2% rate of autism in siblings (as estimated at that time) was far above the general population base rate, and that this suggested a possible high genetic liability, led to the first small-scale twin study of autism. The replicated evidence from both twin and family studies undertaken in the 1970s and 1980s indicated both strong genetic influences and the likelihood that they applied to a phenotype that was much broader than the traditional diagnostic category of autism. Medical and chromosomal findings also indicated genetic heterogeneity. Advances in molecular genetics led to genome-wide scans of affected relative pair samples with a positive log of the odds to base 10 score for a location on chromosome 7. The major remaining research challenges and the likely clinical benefits that should derive from genetic research are considered in relation to both current knowledge and that anticipated to emerge from research over the next decade.

1.3.163. Stoltenberg, S.F., Burmeister, M. **"Recent progress in psychiatric genetics-some hope but no hype."** *Hum Mol Genet* 2000 Apr 12;9(6):927-35. Publication Types: Review, Review, Academic.

Department of Psychiatry, University of Michigan, Ann Arbor 48108, USA.

The reputation of the field of psychiatric genetics has recently become tarnished in the view of many human geneticists. Too many linked loci were claimed and withdrawn, too many association studies published and not confirmed and, more recently, too many new and different chromosomal regions have been implicated for the same disorder. Here, we summarize recent trends, focusing on research that moves away from traditional linkage studies. Some promising strategies include psychopharmacogenetics, and consideration of endophenotypes such as neurophysiological and behavioral markers in addition to the clinical diagnosis. Utilization of rapid and automated methods for scoring genetic variants in large-scale association studies followed by multivariate analyses, which include environmental as well as genetic data, will likely fare better than traditional linkage analysis in disentangling the complex genetics of psychiatric disorders. Some notable areas of recent progress include quantification of the genetic complexity of autism, identification of genetic variants protecting individuals from alcoholism, and the description of several polymorphisms likely to be relevant to behavior and psychiatry. The most notable example may be a common variant that affects the transcription rate in the promoter for the serotonin transporter gene that may be relevant for individual differences in the response to common anti-depressants.

1.3.164. Lamb, J.A., Moore, J., Bailey, A., Monaco, A.P. "Autism: recent molecular genetic advances." *Hum Mol Genet* 2000 Apr 12;9(6):861-8. Publication Types: Review, Review, Tutorial,

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Autism (MIM 209850) is a severe neuropsychiatric disorder of unknown aetiology with profound consequences for patients and their families. Strong evidence from twin and family studies indicates the importance of genetic factors in the development of idiopathic autism, although it is clear that these influences are complex. This review focuses on recent molecular investigations to identify susceptibility loci implicated in autistic disorder.

1.3.165. Kim, S.J., Cook, E.H. Jr. "Novel de novo nonsense mutation of MECP2 in a patient with Rett syndrome." *Hum Mutat* 2000 Apr;15(4):382-3.

Laboratory of Developmental Neuroscience, Department of Psychiatry, University of Chicago, Chicago, Illinois 60637, USA.

Because of the recent identification of several mutations of methyl-CpG-binding protein 2 (MECP2) in patients with Rett syndrome (RTT), a patient with suspected RTT from an autism clinic was screened for mutations. She was found to have a novel heterozygous nonsense mutation, 129C>T (Q19X), which leads to the most severely truncated MECP2 protein reported to date. Sequencing of parental DNA revealed the mutation

was de novo. The patient was not affected with microcephaly or hyperventilation, but had other features of Rett syndrome including severe mental retardation and symptoms of autistic disorder. Moderately skewed X-chromosome inactivation (XCI) may have contributed to her relatively mild phenotype. Copyright 2000 Wiley-Liss, Inc.

1.3.166. Prasad, C., Prasad, A.N., Chodirker, B.N., Lee, C., Dawson, A.K., Jocelyn, L.J., Chudley, A.E. "Genetic evaluation of pervasive developmental disorders: the terminal 22q13 deletion syndrome may represent a recognizable phenotype." *Clin Genet* 2000 Feb;57(2):103-9.

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The evaluation of mental retardation is always a challenge to clinicians. The recognition of specific physical or behavioral characteristics can vastly improve diagnostic yield. Several genetic disorders have been identified to have certain behavioral characteristics, such as Williams syndrome, Smith-Magenis syndrome, and the velocardiofacial syndrome (VCFS). The deletion affecting the chromosome 22q in the most distal band (22q13) appears to define yet another neurobehavioral phenotype. In addition to our report, there are about 17 other cases published of this particular deletion syndrome. We describe three children who share features of developmental delay and pervasive behaviors in addition to normal to advanced growth patterns. Results of cytogenetic analysis suggest that the 3 patients share a deletion affecting the terminal 22q13 region. Two were found to have a cryptic deletion, in the third it was detected by conventional cytogenetics. The cryptic deletions were demonstrated using fluorescent in situ hybridization (FISH), where the control probe for the DiGeorge/VCFS region was deleted. While there remain gaps in our understanding of this particular deletion syndrome, we propose that patients with normal or advanced growth, significantly delayed speech, deviant development and pervasive behaviors, with minor facial dysmorphism, be screened for this deletion.

1.3.167. MacLean, J.E., Teshima, I.E., Szatmari, P., Nowaczyk, M.J. "Ring chromosome 22 and autism: report and review." *Am J Med Genet* 2000 Feb 28;90(5):382-5.

Department of Pathology and Molecular Medicine, McMaster University, and Hamilton Health Sciences Corporation, Ontario, Canada.

Ring chromosome 22 has been described in over 50 cases. A characteristic phenotype has not been fully delineated; however, long face, thick eyebrows, 2-3 toe syndactyly, mental retardation, adequate somatic growth and the absence of major malformations are noted in many cases. An 11-year-old boy with ring chromosome 22 and 46,XY,r(22)(p11.31-q13.31 approximately q13.33) karyotype presented with global developmental delay, autistic disorder, and dolichocephaly, apparently low-set and large ears, midface hypoplasia, and 2-3 toe syndactyly. This is the second report of a ring chromosome 22 with autistic disorder. There appears to be an association between abnormalities of chromosome 22,

including r(22), and autistic disorder; however, this occurrence may be a result of the association of autistic disorder with mental retardation rather than specifically due to r(22). The physical findings in this case also suggest that ring chromosome 22 causes a subtle but distinct phenotype which has previously been proposed.

1.3.168. Kerbeshian, J., Severud, R., Burd, L., Larson, L. "Peek-a-boo fragile site at 16d associated with Tourette syndrome, bipolar disorder, autistic disorder, and mental retardation." *Am J Med Genet* 2000 Feb 7;96(1):69-73.

Department of Neuroscience, University of North Dakota School of Medicine and Health Sciences, Grand Forks, North Dakota, USA.

Five patients with a fragile site at 16q22-23 and neuropsychiatric disorders are reported. Three of five had Tourette disorder, three had mental retardation, two had bipolar disorder, and one had autistic disorder. During our attempts to study the fragile sites in more detail we were unable to reproduce the fragile sites found several years earlier. The potential relationship between the fragile sites and the neuropsychiatric disorders in these patients is discussed. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:69-73, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.169. Martin, E.R., Menold, M.M., Wolpert, C.M., Bass, M.P., Donnelly, S.L., Ravan, S.A., Zimmerman, A., Gilbert, J.R., Vance, J.M., Maddox, L.O., Wright, H.H., Abramson, R.K., DeLong, G.R., Cuccaro, M.L., Pericak-Vance, M.A. "Analysis of linkage disequilibrium in gamma-aminobutyric acid receptor subunit genes in autistic disorder." *Am J Med Genet* 2000 Feb 7;96(1):43-8.

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Autistic disorder (AD) is a neurodevelopmental disorder characterized by abnormalities in behavior, communication, and social interactions and functioning. Recently, Cook et al. reported significant linkage disequilibrium with an AD susceptibility locus and a marker, GABRB3 155CA-2, in the gamma-aminobutyric acid(A) (GABA(A)) receptor beta3-subunit gene on chromosome 15q11-q13. This linkage disequilibrium was detected using a multiallelic version of the transmission/disequilibrium test (TDT) in a sample of nuclear families having at least one child with autistic disorder. In an attempt to replicate this finding we tested for linkage disequilibrium with this marker, as well as with three additional markers in and around the GABA(A) receptor beta3-subunit gene, in an independent, clinically comparable set of AD families. Unlike Cook et al., we failed to detect significant linkage disequilibrium between GABRB3 155CA-2 and AD in our sample. We did, however, find suggestive evidence for linkage disequilibrium with a marker, GABRB3, approximately 60 kb beyond the 3' end of beta3-subunit gene. This finding lends support for previous reports implicating the involvement of genes in this region with AD. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:43-48, 2000 Copyright 2000 Wiley-Liss, Inc.

1.3.170. Ogilvie, C.M., Moore, J., Daker, M., Palferman, S., Docherty, Z. "Chromosome 22q11 deletions are not found in autistic patients identified using strict diagnostic criteria. IMGSAC. International Molecular Genetics Study of Autism Consortium." *Am J Med Genet* 2000 Feb 7;96(1):15-7.

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A group of 103 subjects with a strict diagnosis of autism were tested for deletion of band q11.2 on the long arm of chromosome 22. No deletions were found, indicating that when a patient has been diagnosed with autism using strict and consistent criteria, in the absence of other indications, it is unlikely that this individual will have a 22q11 deletion. Testing for 22q11 deletions is therefore unlikely to be necessary in these patients. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:15-17, 2000. Copyright 2000 Wiley-Liss, Inc.

1.3.171. Gershon, E.S. "Bipolar illness and schizophrenia as oligogenic diseases: implications for the future." *Biol Psychiatry* 2000 Feb 1;47(3):240-4. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, University of Chicago, IL 60637, USA.

As with most complex inheritance diseases, there are at this time no identified susceptibility genes for schizophrenia, bipolar manic-depressive illness, major depression, childhood autism, and other inherited brain disorders whose manifestations are primarily behavioral. Nonetheless, progress has occurred. Genetic epidemiologic research, based on reliable phenotypic definitions, has demonstrated the heritability of many of these disorders. Genetic linkages and associations have been reported and replicated, although there have been inconsistencies between studies, apparently due to the low statistical power of the samples studied to detect small effects genes. Nonreplications of early linkage reports in manic-depressive illness in the 1980s occurred when new cases developed in the same large families in which the linkage was originally reported, and the newly ill persons had the wrong genetic markers in the linkage region. This appears to have resulted from applying inappropriate analytic assumptions of single-gene dominant inheritance of a rare gene, which implied that new cases must arise from the same ancestral gene within the pedigree. When new cases arose in family members not sharing that chromosomal region, the initial linkage report was proved invalid. Under oligogenic inheritance, on the other hand, susceptibility genes are expected to be common, and have a substantial probability of being brought into the pedigree by persons marrying in. Nonspecific psychopathology genes may exist, shared by schizophrenia and bipolar illness, diagnoses which do not co-aggregate in families. The discovery of susceptibility mutations may be expected.

1.3.172. Skuse, D.H. "Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism." *Pediatr Res* 2000 Jan;47(1):9-16. Publication Types: Review, Review, Tutorial.

Institute of Child Health, London, United Kingdom.

Males are at least four times more likely to develop autism than females. Among relatives with a broader autistic phenotype, males predominate too. Autism is a highly heritable disorder, yet genome scans have not revealed any predisposing loci on the sex chromosomes. A nongenetic explanation for male vulnerability, such as exposure to prenatal androgens, is unlikely for a variety of reasons. A novel genetic mechanism that resolves many of the outstanding difficulties is outlined here. The imprinted-X liability threshold model hypothesizes that the threshold for phenotypic expression of many autistic characteristics is influenced by an imprinted X-linked gene(s) that is protective in nature. Imprinted genes are known to play an important role in normal fetal and behavioral development. The gene is expressed only on the X-chromosome that is inherited from the father and raises the threshold for phenotypic expression. It is normally silenced when transmitted maternally. Because only females have a paternal X-chromosome, the threshold for phenotypic expression is higher in them than in males. Evidence for the existence of the genetic locus was found in a study of females with X-monosomy (Turner's syndrome) in which females had either a single paternal or maternal X-chromosome. Identifying the sites of action of this X-linked gene could lead to the discovery of autosomal loci that confer more directly a predisposition to autism.

1.3.173. Zhong, N., Ye, L., Ju, W., Brown, W.T., Tsiouris, J., Cohen, I. "5-HTTLPR variants not associated with autistic spectrum disorders." *Neurogenetics* 1999 Apr;2(2):129-31.

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To determine whether there is an association of polymorphic variants of the serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) and autistic spectrum disorders, we analyzed the 5-HTTLPR genotypes of 72 autistic subjects, 11 fragile X syndrome patients with autistic behavior, 43 normal subjects, and 49 fragile X syndrome non-autistic subjects. The distribution frequency of 5-HTTLPR long allele (L) and the short allele (S) variants showed no differences between subjects. Our findings do not support the hypothesis that polymorphic 5-HTTLPR variants are a susceptibility factor for autistic disorders.

1.3.174. Maddox, L.O., Menold, M.M., Bass, M.P., Rogala, A.R., Pericak-Vance, M.A., Vance, J.M., Gilbert, J.R. "Autistic disorder and chromosome 15q11-q13: construction and analysis of a BAC/PAC contig." *Genomics* 1999 Dec 15;62(3):325-31

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Autistic disorder (AD) is a neurodevelopmental disorder that affects approximately 2-10/10,000 individuals. Chromosome 15q11-q13 has been implicated in the genetic etiology of AD based on (1) cytogenetic abnormalities; (2) increased

recombination frequency in this region in AD versus non-AD families; (3) suggested linkage with markers D15S156, D15S219, and D15S217; and (4) evidence for significant association with polymorphisms in the gamma-aminobutyric acid receptor subunit B3 gene (GABRB3). To isolate the putative 15q11-q13 candidate AD gene, a genomic contig and physical map of the approximately 1.2-Mb region from the GABA receptor gene cluster to the OCA2 locus was generated. Twenty-one bacterial artificial chromosome (BAC) clones, 32 P1-derived artificial chromosome (PAC) clones, and 2 P1 clones have been isolated using the markers D15S540, GABRB3, GABRA5, GABRG3, D15S822, and D15S217, as well as 34 novel markers developed from the end sequences of BAC/PAC clones. In contrast to previous findings, the markers D15S822 and D15S975 have been localized within the GABRG3 gene, which we have shown to be approximately 250 kb in size. NotI and numerous EagI restriction enzyme cut sites were identified in this region. The BAC/PAC genomic contig can be utilized for the study of genomic structure and the identification and characterization of genes and their methylation status in this autism candidate gene region on human chromosome 15q11-q13. Copyright 1999 Academic Press.

1.3.175. Mbarek, O., Marouillat, S., Martineau, J., Barthelemy, C., Muh, J.P., Andres, C. "Association study of the NF1 gene and autistic disorder." *Am J Med Genet* 1999 Dec 15;88(6):729-32.

Laboratoire de Biochimie et de Biologie Moleculaire, INSERM U 316, Tours Cedex, France.

Neurofibromatosis type 1 (NF1) is increased about 150-fold in autistic patients. The aim of this study was to test for an association between the NF1 locus and autistic disorder. The allele distributions of three markers of the NF1 gene were studied in 85 autistic patients and 90 controls. No differences in allele distributions were observed. However, we found a new allele (allele 5) of the GXAlu marker in four autistic patients. Allele 5 was absent in a larger control population (213 individuals). The patients with allele 5 had a more severe clinical picture, mainly in the fields of motility and tonus. Our preliminary results suggest that the NF1 region is not a major susceptibility locus for autism. However, the GXAlu marker of the NF1 gene appears as a possible candidate for a susceptibility locus in a small subgroup of severely affected autistic patients. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 88:729-732, 1999. Copyright 1999 Wiley-Liss, Inc.

1.3.176. Barrett, S., Beck, J.C., Bernier, R., Bisson, E., Braun, T.A., Casavant, T.L., Childress, D., Folstein, S.E., Garcia, M., Gardiner, M.B., Gilman, S., Haines, J.L., Hopkins, K., Landa, R., Meyer, N.H., Mullane, J.A., Nishimura, D.Y., Palmer, P., Piven, J., Purdy, J., Santangelo, S.L., Searby, C., Sheffield, V., Singleton, J., Slager, S., et al. "An autosomal genomic screen for autism. Collaborative linkage study of autism." *Am J Med Genet* 1999 Dec 15;88(6):609-15.

The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Autism is a severe neurodevelopmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are detectable in early childhood. The etiology of idiopathic autism is strongly genetic, and oligogenic transmission is likely. The first stage of a two-stage genomic screen for autism was carried out by the Collaborative Linkage Study of Autism on individuals affected with autism from 75 families ascertained through an affected sib-pair. The strongest multipoint results were for regions on chromosomes 13 and 7. The highest maximum multipoint heterogeneity LOD (MMLS/het) score is 3.0 at D13S800 (approximately 55 cM from the telomere) under the recessive model, with an estimated 35% of families linked to this locus. The next highest peak is an MMLS/het score of 2.3 at 19 cM, between D13S217 and D13S1229. Our third highest MMLS/het score of 2.2 is on chromosome 7 and is consistent with the International Molecular Genetic Study of Autism Consortium report of a possible susceptibility locus somewhere within 7q31-33. These regions and others will be followed up in the second stage of our study by typing additional markers in both the original and a second set of identically ascertained autism families, which are currently being collected. By comparing results across a number of studies, we expect to be able to narrow our search for autism susceptibility genes to a small number of genomic regions. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 88:609-615, 1999. Copyright 1999 Wiley-Liss, Inc.

1.3.177. Ashley-Koch, A., Wolpert, C.M., Menold, M.M., Zaem, L., Basu, S., Donnelly, S.L., Ravan, S.A., Powell, C.M., Qumsiyeh, M.B., Aylsworth, A.S., Vance, J.M., Gilbert, J.R., Wright, H.H., Abramson, R.K., DeLong, G.R., Cuccaro, M.L., Pericak-Vance, M.A. "Genetic studies of autistic disorder and chromosome 7." *Genomics* 1999 Nov 1;61(3):227-36.

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Genome-wide scans have suggested that a locus on 7q is involved in the etiology of autistic disorder (AD). We have identified an AD family in which three sibs inherited from their mother a paracentric inversion in the chromosome 7 candidate region (inv(7)(q22-q31.2)). Clinically, the two male sibs have AD, while the female sib has expressive language disorder. The mother carries the inversion, but does not express AD. Haplotype data on the family suggest that the chromosomal origin of the inversion was from the children's maternal grandfather. Based on these data, we have genotyped 76 multiplex (≥ 2 AD affecteds/family) families for markers in this region of 7q. Two-point linkage analysis yielded a maximum heterogeneity lod score of 1.47 and maximum lod score (MLS) of 1.03 at D7S495. Multipoint MLS and NPL analyses resulted in peak scores of 1.77 at D7S2527 and 2.01 at D7S640. Examination of affected sibpairs revealed significant paternal ($P = 0.007$), but not maternal ($P = 0.75$), identity-by-descent sharing at D7S640. Significant linkage disequilibrium was detected with paternal ($P = 0.02$), but not maternal ($P = 0.15$), transmissions at D7S1824 in multiplex and singleton families. There was also evidence for an increase in recombination in the region (D7S1817 to D7S1824) in the AD families versus non-AD families ($P = 0.03$, sex-averaged;

and $P = 0.01$, sex-specific). These results provide further evidence for the presence of an AD locus on chromosome 7q, as well as provide evidence suggesting that this locus may be paternally expressed. Copyright 1999 Academic Press.

1.3.178. Sukumar, S., Wang, S., Hoang, K., Vanchiere, C.M., England, K., Fick, R., Pagon, B., Reddy, K.S. "Subtle overlapping deletions in the terminal region of chromosome 6q24.2-q26: three cases studied using FISH." *Am J Med Genet* 1999 Nov 5;87(1):17-22. Publication Types: Review, Review of Reported Cases.

Cytogenetics Department, Quest Diagnostics Inc., San Juan Capistrano, California.

Interstitial deletions in the terminal region of chromosome 6 are rare. We describe three new cases with subtle interstitial deletions in the q24-q26 region of the long arm of chromosome 6. The karyotypes were analyzed at a 550 band level. Patient 1 is a 9-month-old boy with an interstitial deletion, del(6)(q24.2q25.1), developmental delay, low birth weight, hypotonia, heart murmur, respiratory distress, craniofacial and genital anomalies. This is the first report of a case with deletion del(6)(q24.2q25.1). Patient 2 is a 17-year-old young man with an interstitial deletion del(6)(q25.1q25.3), developmental delay, short stature, mental retardation, autism, head, face, chest, hand and feet anomalies and a history of seizures. For the first time autism was described as a manifestation in 6q deletions. Patient 3 is baby boy with a de novo interstitial deletion, del(6)(q25.1q26), anomalies of the brain, genital organs, limbs and feet. This is the first report of a case with deletion, del(6)(q25.1q26). In all three patients, fluorescence in situ hybridization (FISH) using chromosome 6 painting probe ruled out an insertion. The ESR (6q25.1) and TBP (6q27) probes were used to confirm the breakpoints. Since TBP signal is present in all cases, it confirmed an interstitial deletion proximal to this probe. Patient 1 has a deletion of the ESR locus; Patient 2 and 3 have signals for the ESR locus on both chromosomes 6. Therefore the deletion in Patients 2 and 3 are between ESR and TBP loci distal to that of Patient 1. FISH validated the deletion breakpoints assessed by conventional cytogenetics. Copyright 1999 Wiley-Liss, Inc.

1.3.179. Amir, R.E., Van den Veyver, I.B., Wan, M., Iran, C.Q., Francke, U., Zoghbi, H.Y. "Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2." *Nat Genet* 1999 Oct;23(2):185-8.

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Rett syndrome (RTT, MIM 312750) is a progressive neurodevelopmental disorder and one of the most common causes of mental retardation in females, with an incidence of 1 in 10,000-15,000 (ref. 2). Patients with classic RTT appear to develop normally until 6-18 months of age, then gradually lose speech and purposeful hand use, and develop microcephaly, seizures, autism, ataxia, intermittent hyperventilation and stereotypic hand movements. After initial regression, the condition stabilizes and patients usually survive into adulthood. As RTT occurs almost exclusively in

females, it has been proposed that RTT is caused by an X-linked dominant mutation with lethality in hemizygous males. Previous exclusion mapping studies using RTT families mapped the locus to Xq28 (refs 6,9,10,11). Using a systematic gene screening approach, we have identified mutations in the gene (MECP2) encoding X-linked methyl-CpG-binding protein 2 (MeCP2) as the cause of some cases of RTT. MeCP2 selectively binds CpG dinucleotides in the mammalian genome and mediates transcriptional repression through interaction with histone deacetylase and the corepressor SIN3A (refs 12,13). In 5 of 21 sporadic patients, we found 3 de novo missense mutations in the region encoding the highly conserved methyl-binding domain (MBD) as well as a de novo frameshift and a de novo nonsense mutation, both of which disrupt the transcription repression domain (TRD). In two affected half-sisters of a RTT family, we found segregation of an additional missense mutation not detected in their obligate carrier mother. This suggests that the mother is a germline mosaic for this mutation. Our study reports the first disease-causing mutations in RTT and points to abnormal epigenetic regulation as the mechanism underlying the pathogenesis of RTT.

1.3.180. Iassig, J.P., Vachirasomtoon, K., Hartzell, K., Leventhal, M., Courchesne, E., Courchesne, R., Lord, C., Leventhal, B.L., Cook, E.H. Jr. "Physical mapping of the serotonin 5-HT(7) receptor gene (HTR7) to chromosome 10 and pseudogene (HTR7P) to chromosome 12, and testing of linkage disequilibrium between HTR7 and autistic disorder." *Am J Med Genet* 1999 Oct 15;88(5):472-5.

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The gene encoding the serotonin 5-HT(7) receptor (HTR7) has been considered as a candidate locus in several neuropsychiatric disorders, based on pharmacological evidence and ligand-binding studies. After determining over 3 kb of previously unpublished sequence from introns 1 and 2 of HTR7, a single base (C/T) polymorphism in the second intron of HTR7 was found. Allele-specific PCR was used to genotype the HTR7 marker in 53 trios consisting of subjects with autistic disorder and both parents. Using the transmission disequilibrium test (TDT), no evidence of preferential transmission of either allele was found (TDT $\chi^2(2) = 0.252$, $p = 0.602$). Sequence data obtained from both intron 1 and intron 2 of HTR7, and from the 5-HT(7) pseudogene (HTR7P), was used to confirm localization of HTR7 to 10q23 and HTR7P to 12p13 using radiation hybrid analyses.

1.3.181. Salmon, B., Hallmayer, J., Rogers, T., Kalaydjieva, I., Petersen, P.B., Nicholas, P., Pingree, C., McMahon, W., Spiker, D., Lotspeich, L., Kraemer, H., McCague, P., Dimiceli, S., Nouri, N., Pitts, T., Yang, J., Hinds, D., Myers, R.M., Risch, N. "Absence of linkage and linkage disequilibrium to chromosome 15q11-q13 markers in 139 multiplex families with autism." *Am J Med Genet* 1999 Oct 15;88(5):551-6.

Centre for Clinical Research in Neuropsychiatry, Graylands Hospital/University of Western Australia, Perth, Australia.

Chromosomal region 15q11-q13 has been implicated to harbor a susceptibility gene or genes underlying autism. Evidence has been derived from the existence of cytogenetic anomalies in this region associated with autism, and the report of linkage in a modest collection of multiplex families. Most recently, linkage disequilibrium with the marker GABRB3-155CA2 in the candidate locus GABRB3, located in this region, has been reported. We searched for linkage using eight microsatellite markers located in this region of chromosome 15 in 147 affected sib-pairs from 139 multiplex autism families. We also tested for linkage disequilibrium in the same set of families with the same markers. We found no evidence for excess allele sharing (linkage) for the markers in this region. Also, we found no evidence of linkage disequilibrium, including for the locus GABRB3-155CA2. Thus, it appears that the role of this region of chromosome 15 is minor, at best, in the majority of individuals with autism.

1.3.182. Konstantareas, M.M., Homatidis, S. "Chromosomal abnormalities in a series of children with autistic disorder." *J Autism Dev Disord* 1999 Aug;29(4):275-85.

University of Guelph, Ontario, Canada.

In a series of 127 children diagnosed with autistic disorder the karyotypes of 8, on whom data were available, showed the following chromosomal abnormalities: breakage, a 47 XY pattern, trisomy 13, inversion-duplication of chromosome 15, 47 XY, +der (15) (pter q15: p11 pter), 47 XXY and 46 XY, inv (2) (p11:q13pat, 3q+). Compared to those who were not karyotyped or had normal karyotypes, the children with abnormalities, although cognitively more delayed, were not rated as more severely autistic. Facial dysmorphias and minor physical anomalies tended to be more frequent in the chromosomally deviant subgroup. No differences in demographic characteristics or parental ages were evident. Results are consistent with the view of variability of expression of marker chromosome deviations and a greater severity of retardation and symptoms of autism in those affected. The relevance of the findings to a multimodal genetic etiology of autistic disorder is discussed.

1.3.183. Hughes, C., Plumet, M.H., Leboyer, M. "Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism." *J Child Psychol Psychiatry* 1999 Jul;40(5):705-18.

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Two studies were conducted to examine executive function skills in siblings of children with autism. In Study 1, four computerised tasks (three executive tasks: the ID/ED set-shifting task; a spatial working memory task; and the Tower of London planning task; and a control spatial span task) from the CANTAB battery were used to compare 31 siblings of children with autism with 32 siblings of children with developmental delay and 32 children from unaffected families. In Study 2, the two sibling groups were compared on two manually administered executive tasks (verbal fluency and

list recall). As a group, autism siblings showed superior spatial and verbal span, but a greater than expected number performed poorly on the set-shifting, planning, and verbal fluency tasks. There were no group differences in working memory performance. The implications of these findings for the broader phenotype of autism is discussed.

1.3.184. Ghaziuddin, M., Burmeister, M. "Deletion of chromosome 2q37 and autism: a distinct subtype?" *J Autism Dev Disord* 1999 Jun;29(3):259-63. Publication Types: Review, Review of Reported Cases.

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Several reports have described the occurrence of chromosome abnormalities in autism, a neuro-developmental disorder characterized by social deficits, communication impairment, and a restricted range of interests. These include the fragile X abnormality and 15q duplications. In this report, we describe two cases of chromosome 2q37 and review the literature on this topic. We propose that deletion of the distal portion of the long arm of chromosome 2 (2q37) may be associated with some cases of autism and with a distinct phenotype. Increased awareness of the dysmorphic features associated with 2q37 deletions may aid in the molecular genetic analysis of this chromosome anomaly and clarify its relationship with autism.

1.3.185. Rogers, T., Kalaydjieva, L., Hallmayer, J., Petersen, P.B., Nicholas, P., Pingree, C., McMahon, W.M., Spiker, D., Lotspeich, L., Kraemer, H., McCague, P., Dimiceli, S., Nouri, N., Peachy, T., Yang, J., Hinds, D., Risch, N., Myers, R.M. "Exclusion of linkage to the HLA region in ninety multiplex sibships with autism." *J Autism Dev Disord* 1999 Jun;29(3):195-201.

Centre for Human Genetics, Edith Cowan University, Perth, Australia.

Several studies have suggested a role for the histocompatibility complex of loci (HLA) in the genetic susceptibility to autism. We have tested this hypothesis by linkage analysis using genetic marker loci in the HLA region on chromosome 6p in multiplex families with autism. We have examined sharing of alleles identical by descent in 97 affected sib pairs from 90 families. Results demonstrate no deviation from the null expectation of 50% sharing of alleles in this region; in fact, for most marker loci, the observed sharing was less than 50%. Thus, it is unlikely that loci in this region contribute to the genetic etiology of autism to any significant extent in our families.

1.3.186. Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J., Kalaydjieva, L., McCague, P., Dimiceli, S., Pitts, T., Nguyen, L., Yang, J., Harper, C., Thorpe, D., Vermeer, S., Young, H., Hebert, J., Lin, A., Ferguson, J., Chiotti, C., Wiese-Slater, S., Rogers, T., Salmon, B., Nicholas, P., Myers, R.M., et al. "A genomic screen of autism: evidence for a multilocus etiology." *Am J Hum Genet* 1999 Aug;65(2):493-507.

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We have conducted a genome screen of autism, by linkage analysis in an initial set of 90 multiplex sibships, with parents, containing 97 independent affected sib pairs (ASPs), with follow-up in 49 additional multiplex sibships, containing 50 ASPs. In total, 519 markers were genotyped, including 362 for the initial screen, and an additional 157 were genotyped in the follow-up. As a control, we also included in the analysis unaffected sibs, which provided 51 discordant sib pairs (DSPs) for the initial screen and 29 for the follow-up. In the initial phase of the work, we observed increased identity by descent (IBD) in the ASPs (sharing of 51.6%) compared with the DSPs (sharing of 50.8%). The excess sharing in the ASPs could not be attributed to the effect of a small number of loci but, rather, was due to the modest increase in the entire distribution of IBD. These results are most compatible with a model specifying a large number of loci (perhaps ≥ 15) and are less compatible with models specifying ≤ 10 loci. The largest LOD score obtained in the initial scan was for a marker on chromosome 1p; this region also showed positive sharing in the replication family set, giving a maximum multipoint LOD score of 2.15 for both sets combined. Thus, there may exist a gene of moderate effect in this region. We had only modestly positive or negative linkage evidence in candidate regions identified in other studies. Our results suggest that positional cloning of susceptibility loci by linkage analysis may be a formidable task and that other approaches may be necessary.

1.3.187. Comi, A.M., Zimmerman, A.W., Frye, V.H., Law, P.A., Pceden, J.N. "Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism." *J Child Neurol* 1999 Jun;14(6):388-94.

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Autism is an age-dependent neurologic disorder that is often associated with autoimmune disorders in the patients' relatives. To evaluate the frequency of autoimmune disorders, as well as various prenatal and postnatal events in autism, we surveyed the families of 61 autistic patients and 46 healthy controls using questionnaires. The mean number of autoimmune disorders was greater in families with autism; 46% had two or more members with autoimmune disorders. As the number of family members with autoimmune disorders increased from one to three, the risk of autism was greater, with an odds ratio that increased from 1.9 to 5.5, respectively. In mothers and first-degree relatives of autistic children, there were more autoimmune disorders (16% and 21%) as compared to controls (2% and 4%), with odds ratios of 8.8 and 6.0, respectively. The most common autoimmune disorders in both groups were type 1 diabetes, adult rheumatoid arthritis, hypothyroidism, and systemic lupus erythematosus. Forty-six percent of the autism group reported having relatives with rheumatoid diseases, as compared to 26% of the controls. Prenatal maternal urinary tract, upper respiratory, and vaginal infections; asphyxia; prematurity, and seizures were more

common in the autistic group, although the differences were not significant. Thirty-nine percent of the controls, but only 11% of the autistic, group, reported allergies. An increased number of autoimmune disorders suggests that in some families with autism, immune dysfunction could interact with various environmental factors to play a role in autism pathogenesis.

1.3.188. Paterson, A.D. "Sixth World Congress of Psychiatric Genetics X Chromosome Workshop." *Am J Med Genet* 1999 Jun 18;88(3):279-86. Publication Types: Congresses.

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At the X chromosome workshop of the Sixth World Congress on Psychiatric Genetics, new data regarding psychiatric phenotypes and the X chromosome were presented. In the last year a number of groups have published linkage results for the X chromosome in schizophrenia, which provide no significant evidence for linkage. Presentations by groups from Cardiff, Oxford, State University of New York (SUNY), and Finland provide weak nonsignificant evidence for linkage of markers on the Xp11.4-p11.3, Xq21, and Xq26 with schizophrenia. However, the presence of a male-specific transmission ratio distorter (DMS1) that maps to Xp11.4-21.2 [Naumova et al., 1998: *Am. J. Hum. Genet.* 62:1493-1499] makes the interpretation of linkage findings in brother-brother pairs difficult in this region. Regarding bipolar affective disorder, little new data were reported, but previous reports provide evidence for linkage to Xq25-q26. Summary tables of linkage results for schizophrenia and bipolar disorder can be obtained from <http://www.camh.net/research/x-chromosome/>. No linkage or transmission disequilibrium of polymorphisms of MAOA and MAOB in attention deficit hyperactivity disorder was seen. Negative results for transmission disequilibrium of polymorphisms of HTR2C and MAOA with autism were provided from German and Austrian families.

1.3.189. Craddock, N., Lendon, C. "Chromosome Workshop: chromosomes 11, 14, and 15." *Am J Med Genet* 1999 Jun 18;88(3):244-54. Publication Types: Congresses.

Division of Neuroscience, University of Birmingham, Queen Elizabeth Psychiatric Hospital, UK. n.craddock@bham.ac.uk

This report describes linkage data presented at the Workshop on Chromosomes 11, 14, and 15 at the Sixth World Congress of Psychiatric Genetics in Bonn, Germany, together with relevant linkage data submitted to the chair and co-chair, and it is presented in the context of the previous literature concerning these chromosomes. We have attempted to collate current linkage data to provide a guide to potentially interesting findings on chromosomes 11, 14, and 15 for the phenotypes of bipolar disorder, schizophrenia, alcoholism, autism, and spelling and reading disability. We discuss methodological limitations and provide chromosome ideograms and tables summarizing findings to date. The most promising region currently appears to be 15q13-q15 in the

region of the alpha 7 nicotinic receptor for the phenotype of schizophrenia (and, perhaps, more generally for functional psychosis). Additionally, 15q11-q13 in the region of GABRB3 holds interest as a potential site of a susceptibility gene for autism. Two regions on chromosome 11, 11p15 in the region of tyrosine hydroxylase gene and 11q22-q23 in the region of DRD2, continue to retain some interest for functional psychosis.

1.3.190. Maclean, J.E., Szatmari, P., Jones, M.B., Bryson, S.E., Mahoney, W.J., Bartolucci, G., Tuff, I. "Familial factors influence level of functioning in pervasive developmental disorder." *J Am Acad Child Adolesc Psychiatry* 1999 Jun;38(6):746-53.

Department of Psychiatry, McMaster University, Hamilton, Ontario, Canada.

OBJECTIVE: To determine whether siblings with pervasive developmental disorders (PDD) tend to have the same type and number of PDD symptoms or a similar level of functioning. **METHOD:** The familial correlations for PDD subtype, symptom totals, adaptive behaviors, and nonverbal IQ were calculated for 94 children with PDD from 46 families. **RESULTS:** On variables measuring PDD symptoms, only impairments in nonverbal communication and verbal/nonverbal status tended to run true within families. There was no familial aggregation of PDD subtype. In contrast, measures of nonverbal IQ and adaptive behaviors in socialization and communication showed a moderate degree of familial resemblance. The degree of familial resemblance did not change if the analysis was restricted only to those families in which both affected children met criteria for autism. **CONCLUSION:** Insofar as the familial resemblance seen in PDD is due to genetic factors, these data provide some evidence that higher- and lower-functioning PDD children may arise from separate genetic mechanisms. Current gene-mapping studies of PDD may need to take this evidence of genetic heterogeneity into account.

1.3.191. Gurrieri, F., Battaglia, A., Torrisi, L., Tancredi, R., Cavallaro, C., Sangiorgi, E., Neri, G. "Pervasive developmental disorder and epilepsy due to maternally derived duplication of 15q11-q13." *Neurology* 1999 May 12;52(8):1694-7.

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Duplications of chromosome 15 have been reported in individuals with atypical autism, varying degrees of mental retardation, and epilepsy. The authors report the molecular analysis, neurophysiologic, and clinical evaluation of a 12-year-old boy with atypical autism and epilepsy due to a maternally derived 15q11-q13 duplication. Their findings suggest that this chromosomal region harbors genes for autism and possibly for partial epilepsy that may act in a dose-dependent manner.

1.3.192. Mannens, M., Alders, M. "**Genomic imprinting: concept and clinical consequences.**" *Ann Med* 1999 Feb;31(1):4-11. Publication Types: Review, Review Literature.

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One of the major discoveries in modern genetics is the phenomenon of genomic, or parental, imprinting. The parent-of-origin effects seen after transmission of an imprinted gene from parents to their children do not follow the genetic rules postulated by Gregor Mendel. This has obvious consequences for genetic counselling. Aberrant imprinting can lead to a wide variety of clinical disorders ranging from the development of tumours to pronounced growth abnormalities and from mental retardation to developmental disorders of language or autism as seen in Turner's syndrome. Here we describe the basic principles of genomic imprinting and discuss a number of well-characterized clinical disorders associated with genomic imprinting.

1.3.193. Szatmari, P. "**Heterogeneity and the genetics of autism.**" *J Psychiatry Neurosci* 1999 Mar;24(2):159-65. Publication Types: Review, Review, Tutorial.

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The objective of this review is to summarize recent data on the genetics of autism, highlight the evidence for genetic heterogeneity and extend the implications of these findings for the identification of susceptibility genes in this disorder. Family studies have shown that autism runs in families and twin studies indicate that the basis of that familial aggregation is genetic. As a result the prospects for the identification of susceptibility genes using either linkage or association studies are quite good. However, recent evidence is accumulating suggesting that the disorder is genetically heterogeneous; higher functioning individuals with autism may arise from separate genetic mechanisms than lower functioning ones. If true, this will make the detection of linkage and association much more difficult.

1.3.194. Trottier, G., Srivastava, L., Walker, C.D. "**Etiology of infantile autism: a review of recent advances in genetic and neurobiological research.**" *J Psychiatry Neurosci* 1999 Mar;24(2):103-15. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Douglas Hospital Research Centre, McGill University, Montreal, Que.

The etiology of autism is complex, and in most cases the underlying pathologic mechanisms are unknown. Autism is a heterogeneous disorder, diagnosed subjectively on the basis of a large number of criteria. Recent research has investigated genetics, in utero insults and brain function as well as neurochemical and immunological factors. On the basis of family and twin studies, there appears to be a genetic basis for a wide "autistic syndrome." About a quarter of cases of autism are associated with genetic disorders such as fragile X syndrome or with infectious diseases such as congenital

rubella. Genetic studies have shown an association between autism markers of brain development such as 3 markers of the c-Harvey-ros oncogene and the homeobox gene EN2. In some cases, autism is associated with insults early in gestation, including thalidomide embryopathy. Autism may arise from abnormal central nervous system functioning, since most autistic patients have indications of brain dysfunction, and about half of them have abnormal electroencephalograms. Similarly, the pattern of evoked response potentials and conduction time is altered in autistic children. There is substantial evidence from neuroimaging studies that dysfunctions in the cerebellum and possibly the temporal lobe and association cortex occur in autistic symptoms. Neurochemical studies have investigated the role of serotonin, epinephrine and norepinephrine, since levels of these neurotransmitters are altered in autism, although other hypotheses implicate overactive brain opioid systems and changes in oxytocin neurotransmission. Autoimmunity may also play a role; antibodies against myelin basic protein are often found in children with autism, who also have increased eosinophil and basophil response to IgE-mediated reactions. In summary, the prevailing view is that autism is caused by a pathophysiologic process arising from the interaction of an early environmental insult and a genetic predisposition.

1.3.195. Piven, J., Palmer, P. "**Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families.**" *Am J Psychiatry* 1999 Apr;156(4):557-63.

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OBJECTIVE: Several studies have shown familial aggregation of some axis I psychiatric disorders in families ascertained through a single autistic proband. In this study the authors examined the rate of axis I psychiatric disorders in nonautistic relatives from multiple-incidence autism families and the possible relationship of these disorders to the broad autism phenotype. **METHOD:** The rates of axis I psychiatric disorders, assessed by using semistructured and family history interviews, were compared in parents, grandparents, and aunts and uncles ascertained through 25 families of multiple-incidence autism probands and 30 families of probands with Down's syndrome. The possible association between selected psychiatric disorders and the broad autism phenotype, assessed directly through semistructured interviews and observational rating measures, was also examined in the two groups of parents. **RESULTS:** The parents of the autistic probands had significantly higher rates of major depressive disorder and social phobia than the parents of the Down's syndrome probands. The high rate of depression in the parents of the autistic probands was consistent with the high rates of depression and anxiety detected in the grandparents and aunts and uncles in the autism families by family history. There was no evidence of an association, within individuals, between either depression or social phobia and the broad autism phenotype. **CONCLUSIONS:** Relatives of autistic individuals have high rates of major depression and

social phobia that are not associated with the broad autism phenotype and cannot be explained by the increased stress associated with raising an autistic child. Alternative mechanisms and the scientific and clinical implications of these findings are discussed.

1.3.196. Philippe, A., Martinez, M., Guilloud-Bataille, M., Gillberg, C., Rastam, M., Sponheim, E., Coleman, M., Zappella, M., Aschauer, H., Van Maldergem, L., Penet, C., Feingold, J., Brice, A., Leboyer, M., van Maldergerme, L. "Genome-wide scan for autism susceptibility genes. Paris Autism Research International Sibpair Study." *Hum Mol Genet* 1999 May;8(5):805-12. Publication Types: Multicenter Study.

INSERM U155, Universite Paris VII, France.

Family and twin studies have suggested a genetic component in autism. We performed a genome-wide screen with 264 microsatellites markers in 51 multiplex families, using non-parametric linkage methods. Families were recruited by a collaborative group including clinicians from Sweden, France, Norway, the USA, Italy, Austria and Belgium. Using two-point and multipoint affected sib-pair analyses, 11 regions gave nominal P-values of 0.05 or lower. Four of these regions overlapped with regions on chromosomes 2q, 7q, 16p and 19p identified by the first genome-wide scan of autism performed by the International Molecular Genetic Study of Autism Consortium. Another of our potential susceptibility regions overlapped with the 15q11-q13 region identified in previous candidate gene studies. Our study revealed six additional regions on chromosomes 4q, 5p, 6q, 10q, 18q and Xp. We found that the most significant multipoint linkage was close to marker D6S283 (maximum lod score = 2.23, P = 0.0013).

1.3.197. Lauritsen, M., Mors, O., Mortensen, P.B., Ewald, H. "Infantile autism and associated autosomal chromosome abnormalities: a register-based study and a literature survey." *J Child Psychol Psychiatry* 1999 Mar;40(3):335-45. Publication Types: Review, Review of Reported Cases.

Department of Psychiatric Demography, Institute for Basic Psychiatric Research, Aarhus University Hospital, Denmark.

Infantile autism is a heterogenous disorder with unknown aetiology. Evidence from the relatively few family and twin studies suggests a genetic component. Co-occurrence or cosegregation between infantile autism and chromosomal abnormalities may identify candidate regions, which could be tested in linkage or association studies. The purpose of this study was to use the Danish Cytogenetic Central Register in order to detect autosomal chromosome abnormalities associated with infantile autism, and to review the literature for cases of autism associated with autosomal chromosome abnormalities to identify candidate chromosomal regions. The register-based study identified possible candidate regions on chromosome 7q21 and 10q21.2, which have not previously been reported. A few interesting candidate regions, 15q11-13, 16q23, and 17p11.2 were found in the literature survey.

1.3.198. Rutter, M., Silberg, J., O'Connor, T., Simonoff, E. "Genetics and child psychiatry: II Empirical research findings." *J Child Psychol Psychiatry* 1999 Jan;40(1):19-55. Publication Types: Review, Review, Academic.

Institute of Psychiatry, London, UK.

Key substantive findings from quantitative and molecular genetic research are reviewed in relation to affective disorder, schizophrenia, autism, hyperkinetic/attention deficit disorder, oppositional and conduct disorders, drug/alcohol problems, and Tourette's syndrome/chronic tics.

1.3.199. Thomas, N.S., Sharp, A.J., Browne, C.E., Skuse, D., Hardie, C., Dennis, N.R. "Xp deletions associated with autism in three females." *Hum Genet* 1999 Jan;104(1):43-8.

Wessex Regional Genetics Laboratory, Salisbury District Hospital, Wilts, UK.

We report eight females with small deletions of the short arm of the X chromosome, three of whom showed features of autism. Our results suggest that there may be a critical region for autism in females with Xp deletions between the pseudoautosomal boundary and DXS7103. We hypothesise that this effect might be due either to the loss of function of a specific gene within the deleted region or to functional nullisomy resulting from X inactivation of the normal X chromosome.

1.3.200. Leboyer, M., Philippe, A., Bouvard, M., Guilloud-Bataille, M., Bondoux, D., Taubateau, F., Feingold, J., Mouren-Simeoni, M.C., Launay, J.M. "Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relatives." *Biol Psychiatry* 1999 Jan 15;45(2):158-63.

INSERM U155, Faculte Jussieu, Paris, France.

BACKGROUND: Whole blood serotonin (5-HT) and C-terminally directed beta-endorphin protein immunoreactivity (C-ter-beta-EP-ir) are known to be elevated in autistic subjects and might be possible markers of genetic liability to autism. This study thus investigates the familial aggregation of 5-HT and of C-ter-beta-EP-ir levels in first degree relatives of autistic probands. METHODS: In a sample of 62 autistic subjects and 122 of their first-degree relatives, compared to age and sex-matched controls, we measured 5-HT by radioenzymology and C-ter-beta-EP-ir by radioimmunoassay. RESULTS: We confirm the previously reported familiarity of hyperserotonemia in autism as mothers (51%), fathers (45%) and siblings (87%) have elevated levels of 5-HT, and we reveal presence of elevated levels of C-ter-beta-EP-ir in mothers (53%) of autistic subjects. CONCLUSIONS: Familial aggregation of quantitative variables, such as concentration of neurotransmitters, within unaffected relative could serve as an intermediate phenotype and might thus help the search of genetic susceptibility factors in autism.

1.3.201. Kleiderlein, J.J., Nisson, P.E., Jessee, J., Li, W.B., Becker, K.G., Derby, M.L., Ross, C.A., Margolis, R.L. "CCG repeats in cDNAs from human brain." *Hum Genet* 1998 Dec;103(6):666-73.

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.

Expansion mutations of trinucleotide repeats and other units of unstable DNA have been proposed to account for at least some of the genetic susceptibility to a number of neuropsychiatric disorders, including bipolar affective disorder, schizophrenia, autism, and panic disorder. To generate additional candidate genes for these and other disorders, cDNA libraries from human brain were probed at high stringency for clones containing CCG, CGC, GCC, CCG, GCG, and GGC repeats (referred to collectively as CCG repeats). Some 18 cDNAs containing previously unpublished or uncharacterized repeats were characterized for chromosomal locus, repeat length polymorphism, and similarity to genes of known function. The cDNAs were also compared with the 37 human genes with eight or more consecutive CCG triplets in GenBank. The repeats were mapped to a number of loci, including 1p34, 2p11.2, 2q30-32, 3p21, 3p22, 4q35, 6q22, 7qter, 13p13, 17q24, 18p11, 19p13.3, 20q12, 20q13.3, and 22q12. Length polymorphism was detected in 50% of the repeats. The newly cloned cDNAs include a complete transcript of human neurexin-1B, a portion of BCNG-1 (a newly described brain-specific ion channel), a previously unreported polymorphic repeat located in the 5' UTR region of the guanine nucleotide-binding protein (G-protein) beta2 subunit, and a human version of the mouse proline-rich protein 7. This list of cDNAs should expedite the search for expansion mutations associated with diseases of the central nervous system.

1.3.202. Volkmar, F.R., Klin, A., Pauls, D. "Nosological and genetic aspects of Asperger syndrome." *J Autism Dev Disord* 1998 Oct;28(5):457-63. Publication Types: Review, Review, Tutorial.

Child Study Center, Yale University, New Haven, Connecticut 06520, USA.

The validity of Asperger syndrome (i.e., apart from high-functioning autism) continues to be the topic of considerable debate. Consistent with Asperger's original description of the condition there appear to be some important potential differences from autism if both conditions are strictly defined. Although the importance of genetic factors in the transmission of autism is increasingly clear it also appears that genetic factors may play an even more important role in Asperger syndrome (AS). The nosological validity of this condition and its relation to the various PDD spectrum disorder remains an important topic for future research. Well-designed and carefully controlled studies are needed in which patterns of comorbidity and associated problems in family members can be carefully assessed. Such studies will contribute to our understanding of the relationship of AS and autism and may clarify important genetic mechanisms of relevance to autism.

1.3.203. Folstein, S.E., Bisson, E., Santangelo, S.L., Piven, J. "Finding specific genes that cause autism: a combination of approaches will be needed to maximize power." *J Autism Dev Disord* 1998 Oct;28(5):439-45. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA.

Although autism is clearly inherited, it may be challenging to find the genes involved: The mechanism of inheritance is unknown, families with an autistic child are usually small, parent-child pairs are rare, and a fairly large number of genes may be involved, some or all of which may have a small effect on the phenotype. We discuss several strategies for finding genes, all of which may be used in combination to find the relevant genes.

1.3.204. Gillberg, C. "Chromosomal disorders and autism." *J Autism Dev Disord* 1998 Oct;28(5):415-25. Publication Types: Review, Review, Tutorial.

Department of Child and Adolescent Psychiatry, University of Goteborg, Sweden.

Many cases of autism appear to be caused by several abnormal genes acting in concert. The literature on chromosomal aberrations in autism is reviewed, with a view to finding potential gene markers for the neuropsychiatric disorder. Most of the chromosomes have been implicated in the genesis of autism. However, aberrations on the long arm of Chromosome 15 and numerical and structural abnormalities of the sex chromosomes have been most frequently reported. These chromosomes appear to hold particular promise in the search for candidate genes.

1.3.205. Bailey, A., Palferman, S., Heavey, L., Le Couteur, A. "Autism: the phenotype in relatives." *J Autism Dev Disord* 1998 Oct;28(5):369-92. Publication Types: Review, Review, Tutorial.

Medical Research Council Child Psychiatry Unit, Institute of Psychiatry, London, United Kingdom.

There is broad agreement that genetic influences are central in the development of idiopathic autism. Whether relatives manifest genetically related milder phenotypes, and if so how these relate to autism proper, has proved a more contentious issue. A review of the relevant studies indicates that relatives are sometimes affected by difficulties that appear conceptually related to autistic behaviors. These range in severity from pervasive developmental disorders to abnormalities in only one area of functioning, and possibly extend to related personality traits. Issues involved in clarifying the components of milder phenotypes and their relationship to autism are outlined.

1.3.206. Szatmari, P., Jones, M.B., Zwaigenbaum, L., MacLean, J.E. "Genetics of autism: overview and new directions." *J Autism Dev Disord* 1998 Oct;28(5):351-68. Publication Types: Review, Review, Tutorial.

McMaster University Medical Centre, Hamilton, Ontario, Canada.

Genetic epidemiology is the study of inherited factors involved in the etiology of a disease or disorder and uses the methods of both medical genetics and clinical epidemiology. In general, genetic epidemiology tries to answer the following

four questions: Is the disorder inherited; What phenotype is inherited; How is it inherited or what is the mode of transmission; and What is the nature of the genetic mutation, if any, that gives rise to the disorder? The hope is that by identifying the gene or genes involved in pathophysiology, a much better understanding of the steps from gene product to phenotype will be possible, leading to improvements in diagnosis, an opportunity for thoughtful family planning, and perhaps, most important, to the development of treatments based on an understanding of the biochemistry of the disorder. We review the current knowledge of the genetic epidemiology of autism and the other pervasive developmental disorders (PDDs) and highlight promising new directions. There seems to be widespread agreement that the PDDs are caused, at least in part, by genetic factors. There is also some agreement on the phenotypic boundaries associated with these same genetic factors. However, many points of uncertainty remain, and several methodologic issues need to be resolved before further progress in mapping susceptibility genes is possible. We do not specifically review molecular studies, medical conditions associated with autism, or the broader autism phenotype, as these topics are covered in other papers in this special issue.

1.3.207. Chudley, A.E., Gutierrez, E., Jocelyn, L.J., Chodirker, B.N. "Outcomes of genetic evaluation in children with pervasive developmental disorder." *J Dev Behav Pediatr* 1998 Oct;19(5):321-5. Publication Types: Clinical Trial.

Section of Genetics and Metabolism, Children's Hospital, Winnipeg, Manitoba, Canada.

We undertook a retrospective etiological study of all children referred for evaluation of pervasive developmental disorder (PDD). We identified 91 children who met the DSM III-R criteria for PDD. Fifty-two were diagnosed with autistic disorder (AD), and 39 with PDD-not otherwise specified (PDD-NOS). Seven families (8.2%) had more than one affected sib. The overall recurrence rate was 7.1%. Six families had a positive history of PDD in more distant relatives. An excess of developmental problems were identified on the maternal side (seven families, vs two families on the paternal side). Affected children had head circumferences above the mean when compared with standardized growth curves. A recognizable syndrome or genetic disorder was identified in 14 children (15.4%), of which 8 children (9%) were thought to be causative of PDD (5 children with Rett syndrome, 2 with fragile X syndrome, and 1 with velocardiofacial syndrome [VCFS]). Six others had a recognized genetic, cytogenetic, or metabolic disorder believed to be unrelated to the PDD diagnosis. Given the relatively high yield of genetic diagnoses in this population, we believe that children with PDD-NOS or AD should have a detailed evaluation by a clinical geneticist or pediatrician trained in dysmorphology. Chromosome anomalies, fragile X, and other recognizable disorders, including VCFS, need to be excluded. The value of general screening for an inborn error of metabolism in all children with PDD is not certain. In light of the relatively high recurrence of PDD in families, genetic counseling is recommended.

1.3.208. Poon, P.M., Chen, Q.L., Lai, K.Y., Wong, C.K., Pang, C.P. "CGG repeat interruptions in the FMR1 gene in patients with infantile autism." *Clin Chem Lab Med* 1998 Aug;36(8):649-53.

Department of Chemical Pathology, Chinese University of Hong Kong, NT.

We determined the CGG repeat length and AGG interruptions in the FMR1 gene in normal Chinese subjects and patients with infantile autism and mild mental retardation. Genomic DNA was investigated by PCR and Southern hybridisation for CGG repeat number and PCR with Mnl I restriction analysis for AGG interruption. Both the normal subjects and the patients with autism have 53 CGG repeats in FMR1, and the majority have two interspersed AGG. Our normal Chinese subjects have a similar number of interspersed AGG as other populations. When compared with the normal subjects, the autism patients have less AGG interruptions and a different pattern of AGG distribution. There was a significant difference in the CGG configurations between normal subjects and patients with autism. The latter had less interspersed AGG, as in fragile X patients, but they did not have fragile X. A study on mentally retarded patients with no infantile autism should also be carried out to ascertain whether mental retardation alone may have contributed to such AGG pattern.

1.3.209. Khan, S.G., Levy, H.L., Legerski, R., Quackenbush, E., Reardon, J.T., Emmert, S., Sancar, A., Li, L., Schneider, T.D., Cleaver, J.E., Kraemer, K.H. "Xeroderma pigmentosum group C splice mutation associated with autism and hypoglycinemia." *J Invest Dermatol* 1998 Nov;111(5):791-6.

Laboratory of Molecular Carcinogenesis, National Cancer Institute, Bethesda, Maryland 20892, USA.

A 4 y old boy of Korean ancestry had xeroderma pigmentosum (XP) with sun sensitivity, multiple cutaneous neoplasms, and inability to speak. Neurologic examination revealed hyperactivity and autistic features without typical XP neurologic abnormalities. Cultured skin fibroblasts (XP22BE) showed decreased post-UV survival, reduced post-UV plasmid host cell reactivation and defective DNA repair (16% of normal unscheduled DNA synthesis in intact cells and undetectable excision repair in a cell free extract). In vitro and in vivo complementation assigned XP22BE to XP group C (XPC) and a markedly reduced level of XPC mRNA was found. Two XPC cDNA bands were identified. One band had a deletion of 161 bases comprising the entire exon 9, which resulted in premature termination of the mutant XPC mRNA. The larger band also had the same deletion of exon 9 but, in addition, had an insertion of 155 bases in its place (exon 9a), resulting in an in-frame XPC mRNA. Genomic DNA analysis revealed a T→G mutation at the splice donor site of XPC exon 9, which markedly reduced its information content. The 155 base pair XPC exon 9a insertion was located in intron 9 and was flanked by strong splice donor and acceptor sequences. Analysis of the patient's blood showed persistently low levels of glycine (68 microM; NL, 125-318 microM). Normal glycine levels were maintained with oral glycine supplements and his hyperactivity diminished. These data

provide evidence of an association of an XPC splice site mutation with autistic neurologic features and hypoglycemia.

1.3.210. Zilbovicius, M., Boddaert, N., Belin, P., Poline, J.B., Remy, P., Mangin, J.F., Thivard, L., Barthelemy, C., Samson, Y. **"Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography."**

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OBJECTIVE: The nature of the underlying brain dysfunction of childhood autism, a life-long severe developmental disorder, is not well understood. Although researchers using functional brain imaging have attempted to contribute to this debate, previous studies have failed to report consistent localized neocortical brain dysfunction. The authors reasoned that early methods may have been insensitive to such dysfunction, which may now be detectable with improved technology. **METHOD:** To test this hypothesis, regional

cerebral blood flow was measured with positron emission tomography (PET) in 21 children with primary autism and in 10 nonautistic children with idiopathic mental retardation. Autistic and comparison groups were similar in average age and developmental quotients. The authors first searched for focal brain dysfunction in the autistic group by using a voxel-based whole brain analysis and then assessed the sensitivity of the method to detect the abnormality in individual children. An extension study was then performed in an additional group of 12 autistic children. **RESULTS:** The first autistic group had a highly significant hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex, which was detected in 76% of autistic children. Virtually identical results were found in the second autistic group in the extension study. **CONCLUSIONS:** PET and voxel-based image analysis revealed a localized dysfunction of the temporal lobes in school-aged children with idiopathic autism. Further studies will clarify the relationships between these temporal abnormalities and the perceptive, cognitive, and emotional developmental abnormalities characteristic of this disorder.

EPIDEMIOLOGY -

**Prevalance, Incidence,
Course and Prognosis**

2.1. Lingam, R., Simmons, A., Andrews, N., Miller, E., Stowe, J., Taylor, B. "Prevalence of autism and parentally reported triggers in a north east London population." *Arch Dis Child*. 2003 Aug;88(8):666-70.

Centre for Community Child Health, Royal Free and University College Medical School, Royal Free Campus, University College London, London NW3 2PF.

BACKGROUND: The recorded prevalence of autistic spectrum disorders has risen over recent decades. Measles, mumps and rubella (MMR) vaccine has been blamed, by causing a "new variant" form of "regressive autism" associated with "autistic enterocolitis". **AIMS:** To estimate the prevalence of autism and to assess any changes in parental perception regarding the onset or causes of autism. **METHODS AND RESULTS:** A total of 567 children with autistic spectrum disorder in five districts in north east London were identified, born 1979-98. Reported autism, excluding the 94 cases of Asperger's syndrome, increased by year of birth until 1992, since when prevalence has plateaued. This flattening off persisted after allowing for expected delay in diagnosis in more recent birth cohorts. The age at diagnosis of autistic spectrum disorder was estimated to have decreased per five year period since 1983, by 8.7% for childhood autism and by 11.0% for atypical autism. There was some evidence that MMR was more likely to be mentioned as a trigger after August 1997 than before. **CONCLUSIONS:** The prevalence of autism, which was apparently rising from 1979 to 1992, reached a plateau from 1992 to 1996 at a rate of some 2.6 per 1000 live births. This levelling off, together with the reducing age at diagnosis, suggests that the earlier recorded rise in prevalence was not a real increase but was likely due to factors such as increased recognition, a greater willingness on the part of educationalists and families to accept the diagnostic label, and better recording systems. The proportion of parents attributing their child's autism to MMR appears to have increased since August 1997.

2.2. Gurney, J.G., Fritz, M.S., Ness, K.K., Sievers, P., Newschaffer, C.J., Shapiro, E.G. "Analysis of prevalence trends of autism spectrum disorder in Minnesota." *Arch Pediatr Adolesc Med*. 2003 Jul;157(7):622-7.

Divisions of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis 55455, USA. gurney@epi.umn.edu

BACKGROUND: Alarming increases in the prevalence of autism spectrum disorder have been reported recently in the United States and Europe. **OBJECTIVES:** To quantify and characterize prevalence trends over time in autism spectrum disorder in Minnesota. **METHODS:** We conducted an age-period-birth cohort analysis of special educational disability data from the Minnesota Department of Children, Families & Learning from the 1981-1982 through the 2001-2002 school years. **RESULTS:** Prevalence rates of autism spectrum disorder rose substantially over time within single-age groups and increased from year to year within birth cohorts. Autism spectrum disorder prevalence among children aged 6 to 11 years increased from 3 per 10 000 in 1991-1992 to 52 per 10

000 in 2001-2002. All other special educational disability categories also increased during this period, except for mild mental handicap, which decreased slightly from 24 per 10 000 to 23 per 10 000. We found that federal and state administrative changes favoring identification of autism spectrum disorders corresponded in time with the increasing rates. **CONCLUSIONS:** We observed dramatic increases in the prevalence of autism spectrum disorder as a primary special educational disability starting in the 1991-1992 school year, and the trends show no sign of abatement. We found no corresponding decrease in any special educational disability category to suggest diagnostic substitution as an explanation for the autism trends in Minnesota. We could not assess changes in actual disease incidence with these data, but federal and state administrative changes in policy and law favoring better identification and reporting of autism are likely contributing factors to the prevalence increases and may imply that autism spectrum disorder has been underdiagnosed in the past.

2.3. Webb, E., Morey, J., Thompson, W., Butler, C., Barber, M., Fraser, W.I. "Prevalence of autistic spectrum disorder in children attending mainstream schools in a Welsh education authority." *Dev Med Child Neurol*. 2003 Jun;45(6):377-84.

Department of Child Health, University of Wales College of Medicine, Children's Centre, Cardiff, UK. webbev@cf.ac.uk

All mainstream primary schools in Cardiff were invited in July 1998 to participate in a prevalence survey of autistic spectrum disorder. Teachers of each class filled in a questionnaire based on ICD-10 criteria for autistic disorders. The Autism Spectrum Screening Questionnaire (ASSQ) was completed on children identified with problems identified by the questionnaire. A total of 11692 children born between 1 September 1986 and 31 August 1990 were screened: 234 (2%) children were identified as requiring an ASSQ; 151 of 234 (65%) ASSQs were returned. Of the 151, 60 children (52 male, 8 female; 40%) scored 22 or more. Their notes and the involved professionals were consulted. Thirty-five children, unknown to specialist services or with complex features, required additional assessment. Seventeen children (all male) were found to be on the autistic spectrum. When the overall rubric was disentangled we found a diverse population of affected children including a handful who did not fit easily into ICD-10 classification. Correcting for incomplete ascertainment we found a minimum prevalence of 20.2 out of every 10 000 (SE = 4.5) for autistic spectrum disorder in this population.

2.4. Constantino, J.N., Todd, R.D. "Autistic traits in the general population: a twin study." *Arch Gen Psychiatry*. 2003 May;60(5):524-30. Publication Types: Twin Study.

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BACKGROUND: Recent research has indicated that autism is not a discrete disorder and that family members of autistic probands have an increased likelihood of exhibiting autistic

symptoms with a wide range of severity, often below the threshold for a diagnosis of an autism spectrum disorder. OBJECTIVE: To examine the distribution and genetic structure of autistic traits in the general population using a newly established quantitative measure of autistic traits, the Social Responsiveness Scale (formerly known as the Social Reciprocity Scale). METHODS: The sample consisted of 788 pairs of twins aged 7 to 15 years, randomly selected from the pool of participants in a large epidemiologic study (the Missouri Twin Study). One parent of each pair of twins completed the Social Responsiveness Scale on each child. The data were subjected to structural equation modeling. RESULTS: Autistic traits as measured by the Social Responsiveness Scale were continuously distributed and moderately to highly heritable. Levels of severity of autistic traits at or above the previously published mean for patients with pervasive developmental disorder not otherwise specified were found in 1.4% of boys and 0.3% of girls. Structural equation modeling revealed no evidence for the existence of sex-specific genetic influences, and suggested specific mechanisms by which females may be relatively protected from vulnerability to autistic traits. CONCLUSIONS: These data indicate that the social deficits characteristic of autism spectrum disorders are common. Given the continuous distribution of these traits, it may be arbitrary where cutoffs are made between research designations of being "affected" vs "unaffected" with a pervasive developmental disorder. The genes influencing autistic traits appear to be the same for boys and girls. Lower prevalence (and severity) of autistic traits in girls may be the result of increased sensitivity to early environmental influences that operate to promote social competency.

2.5. Prior, M. "Is there an increase in the prevalence of autism spectrum disorders?" *J Paediatr Child Health*. 2003 Mar;39(2):81-2. Publication Types: Review, Review, Tutorial.

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This report summarizes recent prevalence estimates for autism spectrum disorders and outlines possible reasons for an apparent increase in the numbers of children diagnosed with autism and Asperger syndrome.

2.6. Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C., Murphy, C. "Prevalence of autism in a US metropolitan area." *JAMA*. 2003 Jan 1;289(1):49-55.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (F-15), 4770 Buford Hwy NE, Atlanta, GA 30341, USA. mxy1@cdc.gov

CONTEXT: Concern has been raised about possible increases in the prevalence of autism. However, few population-based studies have been conducted in the United States. OBJECTIVES: To determine the prevalence of autism among children in a major US metropolitan area and to describe characteristics of the study population. DESIGN, SETTING,

AND POPULATION: Study of the prevalence of autism among children aged 3 to 10 years in the 5 counties of metropolitan Atlanta, Ga, in 1996. Cases were identified through screening and abstracting records at multiple medical and educational sources, with case status determined by expert review. MAIN OUTCOME MEASURES: Autism prevalence by demographic factors, levels of cognitive functioning, previous autism diagnoses, special education eligibility categories, and sources of identification. RESULTS: A total of 987 children displayed behaviors consistent with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for autistic disorder, pervasive developmental disorder-not otherwise specified, or Asperger disorder. The prevalence for autism was 3.4 per 1000 (95% confidence interval [CI], 3.2-3.6) (male-female ratio, 4:1). Overall, the prevalence was comparable for black and white children (black, 3.4 per 1000 [95% CI, 3.0-3.7] and white, 3.4 per 1000 [95% CI, 3.2-3.7]). Sixty-eight percent of children with IQ or developmental test results (N = 880) had cognitive impairment. As severity of cognitive impairment increased from mild to profound, the male-female ratio decreased from 4.4 to 1.3. Forty percent of children with autism were identified only at educational sources. Schools were the most important source for information on black children, children of younger mothers, and children of mothers with less than 12 years of education. CONCLUSION: The rate of autism found in this study was higher than the rates from studies conducted in the United States during the 1980s and early 1990s, but it was consistent with those of more recent studies.

2.7. Charman, T. "The prevalence of autism spectrum disorders. Recent evidence and future challenges." *Eur Child Adolesc Psychiatry*. 2002 Dec;11(6):249-56.

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BACKGROUND: Until recently best estimate prevalence rates for autism spectrum disorders (ASD) were 0.5/1,000 for autism and 2.0/1,000 for the broader spectrum. Three recent studies have suggested a significantly higher prevalence rate for ASD of 6.0/1,000 (mean 95 % CI = 4.8-8.0). METHOD: Possible determinants of the apparent increase in the prevalence of ASD are outlined. Methodological aspects of the three recent studies are examined. FINDINGS: Increased recognition, the broadening of the diagnostic concept over time and methodological differences across studies may account for most or all of the apparent increase in prevalence, although this cannot be quantified. CONCLUSIONS: Findings from ongoing studies should help confirm or disconfirm the putative rate of 6.0/1,000 for all ASD. The possibility that autism has been over-diagnosed in recent studies needs to be ruled out. Notwithstanding these outstanding questions, it appears likely that the current true prevalence of ASD is considerably greater than previously recognised. This has significant implications for our scientific understanding of ASD and for families and services. Future directions for epidemiological research are outlined.

2.8. Wing, L., Potter, D. "The epidemiology of autistic spectrum disorders: is the prevalence rising?" *Ment Retard Dev Disabil Res Rev* 2002;8(3):151-61. Publication Types: Review, Review, Tutorial.

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For decades after Kanner's original paper on the subject was published in 1943, autism was generally considered to be a rare condition with a prevalence of around 2-4 per 10,000 children. Then, studies carried out in the late 1990s and the present century reported annual rises in incidence of autism in pre-school children, based on age of diagnosis, and increases in the age-specific prevalence rates in children. Prevalence rates of up to 60 per 10,000 for autism and even more for the whole autistic spectrum were reported. Reasons for these increases are discussed. They include changes in diagnostic criteria, development of the concept of the wide autistic spectrum, different methods used in studies, growing awareness and knowledge among parents and professional workers and the development of specialist services, as well as the possibility of a true increase in numbers. Various environmental causes for a genuine rise in incidence have been suggested, including the triple vaccine for measles, mumps and rubella (MMR). Not one of the possible environmental causes, including MMR, has been confirmed by independent scientific investigation, whereas there is strong evidence that complex genetic factors play a major role in etiology. The evidence suggests that the majority, if not all, of the reported rise in incidence and prevalence is due to changes in diagnostic criteria and increasing awareness and recognition of autistic spectrum disorders. Whether there is also a genuine rise in incidence remains an open question. Copyright 2002 Wiley-Liss, Inc.

2.9. Fiona, J.S., Baron-Cohen, S., Bolton, P., Brayne, C. "Brief report: prevalence of autism spectrum conditions in children aged 5-11 years in Cambridgeshire, UK." *Autism* 2002 Sep;6(3):231-7.

Autism Research Centre, University of Cambridge, Department of Psychiatry, UK.

The study aimed to establish prevalence of the broader autistic spectrum, including Asperger syndrome, in 5- to 11-year-olds in Cambridgeshire, UK. Cases of diagnosed autism spectrum condition (ASC) in children who were in Cambridgeshire schools and aged between 5 and 11 years on 31 December 1999 were sought using public records, screening instruments, educational psychology and special educational needs coordinator (SENCO) records. We report a prevalence of ASC in the age group 5-11 years of almost 0.6 percent (57 in 10,000). This is 11 times higher than the rate of classic autism but in line with other recent national and international rates for the broader spectrum. In the responding mainstream schools the prevalence was 0.33 percent. In the responding special school population it was 12.5 percent. The overall sex ratio of the children with ASC replicated findings for classical autism of 4:1 (M:F), but in those children being educated in mainstream schools the sex ratio was 8:1 (M:F).

2.10. Kidd, P.M. "Autism, an extreme challenge to integrative medicine. Part 1: The knowledge base." *Altern Med Rev* 2002 Aug;7(4):292-316. Publication Types: Review, Review, Tutorial.

Autism, archetype of the autistic spectrum disorders (ASD), is a neurodevelopmental disorder characterized by socially aloof behavior and impairment of language and social interaction. Its prevalence has surged in recent years. Advanced functional brain imaging has confirmed pervasive neurologic involvement. Parent involvement in autism management has accelerated understanding and treatment. Often accompanied by epilepsy, cognitive deficits, or other neurologic impairment, autism manifests in the first three years of life and persists into adulthood. Its etiopathology is poorly defined but likely multifactorial with heritability playing a major role. Prenatal toxic exposures (teratogens) are consistent with autism spectrum symptomatology. Frequent vaccinations with live virus and toxic mercurial content (thimerosal) are a plausible etiologic factor. Autistic children frequently have abnormalities of sulfoxidation and sulfation that compromise liver detoxification, which may contribute to the high body burden of xenobiotics frequently found. Frequent copper-zinc imbalance implies metallothionein impairment that could compound the negative impact of sulfur metabolism impairments on detoxification and on intestinal lining integrity. Intestinal hyperpermeability manifests in autistic children as dysbiosis, food intolerances, and exorphin (opioid) intoxication, most frequently from casein and gluten. Immune system abnormalities encompass derangement of antibody production, skewing of T cell subsets, aberrant cytokine profiles, and other impairments consistent with chronic inflammation and autoimmunity. Coagulation abnormalities have been reported. Part 2 of this review will attempt to consolidate progress in integrative management of autism, aimed at improving independence and lifespan for people with the disorder.

2.11. Croen, L.A., Grether, J.K., Selvin, S. "Descriptive epidemiology of autism in a California population: who is at risk?" *J Autism Dev Disord* 2002 Jun;32(3):217-24.

March of Dimes Birth Defects Foundation/California Department of Health Services, California Birth Defects Monitoring Program, Oakland 94606-5226, USA. Lisa.A.Croen@kp.org

We investigated the association between selected infant and maternal characteristics and autism risk. Children with autism born in California in 1989-1994 were identified through service agency records and compared with the total population of California live births for selected characteristics recorded on the birth certificate. Multivariate models were used to generate adjusted risk estimates. From a live birth population of more than 3.5 million, 4381 children with autism were identified. Increased risks were observed for males, multiple births, and children born to black mothers. Risk increased as maternal age and maternal education increased. Children born to immigrant mothers had similar or decreased risk compared with California-born mothers. Environmental factors associated with these demographic characteristics may interact with genetic vulnerability to increase the risk of autism.

2.12. Croen, L.A., Grether, J.K., Hoogstrate, J., Selvin, S. "The changing prevalence of autism in California." *J Autism Dev Disord* 2002 Jun;32(3):207-15.

March of Dimes Birth Defects Foundation/California Department of Health Services, California Birth Defects Monitoring Program, Oakland 94606-5226, USA. Lisa.A.Croen@kp.org

We conducted a population-based study of eight successive California births cohorts to examine the degree to which improvements in detection and changes in diagnosis contribute to the observed increase in autism prevalence. Children born in 1987-1994 who had autism were identified from the statewide agency responsible for coordinating services for individuals with developmental disabilities. To evaluate the role of diagnostic substitution, trends in prevalence of mental retardation without autism were also investigated. A total of 5038 children with full syndrome autism were identified from 4,590,333 California births, a prevalence of 11.0 per 10,000. During the study period, prevalence increased from 5.8 to 14.9 per 10,000, for an absolute change of 9.1 per 10,000. The pattern of increase was not influenced by maternal age, race/ethnicity, education, child gender, or plurality. During the same period, the prevalence of mental retardation without autism decreased from 28.8 to 19.5 per 10,000, for an absolute change of 9.3 per 10,000. These data suggest that improvements in detection and changes in diagnosis account for the observed increase in autism; whether there has also been a true increase in incidence is not known.

2.13. Fombone, E. "Prevalence of childhood disintegrative disorder." *Autism* 2002 Jun;6(2):149-57. Publication Types: Review, Review Literature.

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The prevalence of childhood disintegrative disorder (CDD) is unknown. In this study, 32 epidemiological surveys of autism and pervasive developmental disorders published in English language journals since 1966 were reviewed. Four surveys yielded estimates for CDD ranging from 1.1 to 6.4 per 100,000 subjects. A pooled estimate across these four surveys is 1.7 per 100,000 (95 percent Confidence Interval: 0.6-3.8 per 100,000). The conclusion is that CDD is very rare and its prevalence is 60 times less than that for autistic disorder, assuming a prevalence of 10 per 10,000 for autism. If a rate of 30 per 10,000 is taken for all PDDs, only one child out of 175 children with a PDD diagnosis would, on average, meet criteria for CDD.

2.14. Shavelle, R.M., Strauss, D.J., Pickett, J. "Causes of death in autism." *J Autism Dev Disord* 2001 Dec;31(6):569-76.

Life Expectancy Project, San Francisco, California, USA.

The objective of this study was to determine which causes of death are more frequent in persons with autism, and by how much, compared with the general population. Subjects were 13,111 ambulatory Californians with autism, followed between 1983 and 1997. The units of study were person-years, each

linked to the subject's age, sex, and cause of death (if any) for the specific year. Observed numbers of cause-specific deaths were compared with numbers expected according to general population mortality rates. Standardized mortality rates (SMRs) were computed for each mental retardation level. Elevated death rates were observed for several causes, including seizures and accidents such as suffocation and drowning; elevated mortality due to respiratory disease was observed among persons with severe mental retardation. Overall, excess mortality was especially marked for persons with severe mental retardation, but life expectancy is reduced even for persons who are fully ambulatory and who have only mild mental retardation.

2.15. Gabries, R.L., Hill, D.E., Pierce, R.A., Rogers, S.J., Wehner, B. "Predictors of treatment outcome in young children with autism: a retrospective study." *Autism* 2001 Dec;5(4) : 407-29.

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This study examined predictors of developmental outcomes in 17 children diagnosed with autism or PDD - NOS, who received generic treatment over a mean period of 37 months. Pre-treatment evaluations occurred at a mean age of 31 months with follow-up evaluations at a mean age of 69 months. Significantly different developmental trajectories were observed among the participants at follow-up, separating the participants into two distinct groups (high and low outcome). However, groups did not differ significantly in treatment intensity or other outcome prediction measures. Pre-treatment developmental intelligence levels between the two groups approached significance. The results raise questions regarding the effect of treatment intensity and type, family stress factors, and intelligence ability in very early childhood on outcome.

2.16. Rasmussen, P., Borjesson, O., Wentz, E., Gillberg, C. "Autistic disorders in Down syndrome: background factors and clinical correlates." *Dev Med Child Neurol* 2001 Nov;43(11) :750-4.

Institute for the Health of Women and Children, Department of Child and Adolescent Psychiatry, University of Goteburg, Sweden. ann.nordstrom@pediat.gu.se

A study of a clinic-based sample of 25 individuals (12 females, 13 males; age at diagnosis 14.4 years, SD 7.4 Years; age range 4 to 33 years) with down syndrome (DS) and autism is by no means rare in DS. Results showed that there was a considerable delay in the diagnosis of autism as compared with children with autism who did not have DS. In 11 participants medical factors were identified that were likely to be of importance in contributing to the development of autism, and in four further participants there were factors of possible significance. Such factors include a history of autism or autism-related disorders in first- or- second-degree relatives (n=5), infantile spasms (n=5), early hypothyroidism (n=3), evidence of brain injury after complicated heart surgery (n=2), or a combination of these factors. It is important that autism is recognized, identified, and fully assessed in

individuals with DS in order for them to receive appropriate education and support.

2.17. Bernabei, P., Camaioni, L. "Developmental profile and regression in a child with autism : a single case study." *Autism* 2001 Sep; 5(3) : 287-97.

Department of Childhood Neurological and Psychiatric Sciences, University of Rome La Sapienza, Italy. pbernabei@uniroma1.it

The developmental profile of a child with autism during the first 3 years of life is presented. Clinical material obtained from different sources is discussed : home videos from birth to 3 years and cognitive and communicative evaluations at 24, 34 and 38 months. The videos show how the child appeared to make progress up to 12 months, but from 12 to 18 months some abilities that had been previously acquired were lost, and a decrease in social interaction, communicative and linguistic abilities remained unchanged, but social interactive behaviours continued to decrease. The particular profile identified is discussed as one of the possible pathways through which autism may develop.

2.18. Wheelwright, S., Baron-Cohen, S. "The link between autism and skills such as engineering, maths, physics and computing: a reply to Jarrold and Routh." *Autism* 2001 Jun;5(2) :223-7.

Autism Research Centre, Department of Experimental Psychology, University of Cambridge, UK.

In the first edition of this journal, we published a paper reporting that fathers and grandfathers of children with autism were over-represented in the field of engineering. This result was interpreted as providing supporting evidence for the folk-psychology/folk-physics theory of autism. After carrying out further analysis on the same data, Jarrold and Routh found that fathers of children with autism were also over-represented in accountancy and science. They suggested that these results could either provide additional support for the folk-psychology/ folk-physics theory or be accounted for by an over-representation of professionals amongst the fathers of children with autism. Here we present evidence that engineers are still over-represented among fathers of children with autism, even taking into account the professional bias.

2.19. Bertrand, J., Mars, A., Boyle, C., Bove, F., Yeorginn -allsopp, M., Decoufle, P. "Prevalence of autism in a United States population : the Brick Township, New Jersey, investigation." *Pediatrics* 2001 Nov ; 108 (5) : 1155-61.

National Centre on Birth Defects and Developmental Disabilities, Centres for Disease Control and Prevention, Atlanta, Georgia 30341, USA. jbertrand@cdc.gov

OBJECTIVE: This study determined the prevalence of autism for a defined community, Brick Township, New Jersey, using current diagnostic and epidemiologic methods. **METHODS:** The target population was children who were 3 to 10 years of age in 1998, who were residents of brick Township at any point during that year, and who had an autism spectrum disorder. Autism spectrum disorder -not otherwise specified

(PDD-NOS), and Asperger disorder. The study used 4 sources for active case finding: special education records, records from local clinicians providing diagnosis or treatment for developmental or behavioral disabilities, lists of children from community parent groups, and families who autism diagnosis was verified for participation in the study in response to media attention. The clinical assessment. The assessment included medical and developmental history, functioning and administration of the Autism Diagnostic Observation Schedule-Generic. **RESULTS:** The prevalence of all autism spectrum disorders combined was 6.7 cases per 1000 children. The prevalence for children whose condition met full diagnostic criteria for autistic disorder was 4.0 cases per 1000 children, and the prevalence for PDD-NOS and Asperger disorder was 2.7 cases per 1000 children. Characteristics of children with autism in this study were similar to those in previous studies of autism. **CONCLUSIONS:** The prevalence of autism in Brick Township seems to be higher than that in other studies, particularly studies conducted in the United States, but within the range of a few recent studies conducted in the United States, but within the range of a few recent studies in smaller population that used more through case-finding methods.

2.20. Tolbert, L., Brown, R., Fowler, P., Parsons, D. "Brief report: Lack of correlation between age of symptom onset and contemporaneous presentation." *J Autism Dev Disord* 2001 Apr;31(2):241-5.

Glenwood Incorporated, and The University of Alabama at Birmingham, 35294-0017, USA. Itolbert@psych.uabmc.edu

The parents/guardians of 50 individuals were surveyed using a semistructured interview to determine the feasibility of this method and to establish ages of symptom onset. Thirty-eight informants were able to recall sufficient detail to allow categorization of the age of symptom onset. Chi-square analysis confirmed a significant association between investigators' categorization and informants' categorization. Contemporaneous presentation was indexed using Childhood Autism Rating Scale, the Autism Behavior Checklist, the Conners Hyperactivity Index, and the Ritvo-Freeman Real Life Rating Scale for Autism. No significant correlations were determined between any of these indices of symptom severity and age of symptom onset.

2.21. Magnusson, P., Saemundsen, E. "Prevalence of autism in Iceland." *J Autism Dev Disord* 2001 Apr;31(2):153-63.

Department of Child and Adolescent Psychiatry, National University Hospital, Reykjavik, Iceland. pama@landspitali.is

This clinic-based study estimated the prevalence of autism in Iceland in two consecutive birth cohorts, subjects born in 1974-1983 and in 1984-1993. In the older cohort classification was based on the ICD-9 in 72% of cases while in the younger cohort 89% of cases were classified according to the ICD-10. Estimated prevalence rates for Infantile autism/Childhood autism were 3.8 per 10,000 in the older cohort and 8.6 per 10,000 in the younger cohort. The characteristics of the autistic groups are presented in terms of level of intelligence,

male:female ratio, and age at diagnosis. For the younger cohort scores on the Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale are reported as well. Results are compared with a previous Icelandic study and recent population-based studies in other countries based on the ICD-10 classification system. Methodological issues are discussed as well as implications for future research and service delivery.

2.22. Chakrabarti, S., Fombonne, E. "Pervasive developmental disorders in preschool children." *JAMA* 2001 Jun 27;285(24):3093-9.

MRC Child Psychiatry Unit, Institute of Psychiatry/King's College London, Denmark Hill, London SE5 8AF, England.

CONTEXT: Prevalence rates of autism-spectrum disorders are uncertain, and speculation that their incidence is increasing continues to cause concern. OBJECTIVE: To estimate the prevalence of pervasive developmental disorders (PDDs) in a geographically defined population of preschool children. DESIGN, SETTING, AND PARTICIPANTS: Survey conducted July 1998 to June 1999 in Staffordshire, England. The area's 15 500 children aged 2.5 to 6.5 years were screened for developmental problems. Children with symptoms suggestive of a PDD were intensively assessed by a multidisciplinary team, which conducted standardized diagnostic interviews and administered psychometric tests. MAIN OUTCOME MEASURE: Prevalence estimates for subtypes of PDDs. RESULTS: A total of 97 children (79.4% male) were confirmed to have a PDD. The prevalence of PDDs was estimated to be 62.6 (95% confidence interval, 50.8-76.3) per 10 000 children. Prevalences were 16.8 per 10 000 for autistic disorder and 45.8 per 10 000 for other PDDs. The mean age at diagnosis was 41 months, and 81% were originally referred by health visitors (nurse specialists). Of the 97 children with a PDD, 25.8% had some degree of mental retardation and 9.3% had an associated medical condition. CONCLUSIONS: Our results suggest that rates of PDD are higher than previously reported. Methodological limitations in existing epidemiological investigations preclude interpretation of recent high rates as indicative of increased incidence of these disorders although this hypothesis requires further rigorous testing. Attention is nevertheless drawn to the important needs of a substantial minority of preschool children.

2.23. Johansson, M., Wentz, E., Fernell, E., Stromland, K., Miller, M.T., Gillberg, C. "Autistic spectrum disorders in Mobius sequence: a comprehensive study of 25 individuals." *Dev Med Child Neurol* 2001 May;43(5):338-45.

Department of Child and Adolescent Psychiatry, Goteborg University, Sweden. maria.johansson@pediat.gu.se

The prevalence of autistic disorder was analysed in 25 individuals with Mobius sequence, a disorder with brain-stem dysfunction. The sample consisted of 18 males and seven females (20 participants were aged 2 to 22 years, and five were aged 1, 19 and 23 months, and 55 years old). Participants were recruited after a nationwide call and were part of a multidisciplinary study of individuals with Mobius sequence.

They were given a meticulous neuropsychiatric examination including standardized autism diagnostic interviews. Ten individuals had an autistic spectrum disorder. Six of these met all diagnostic criteria for autism. In 23 individuals cognitive development could be assessed. Eight of those 23 patients had clear learning disability and six individuals were functioning in the normal but subaverage range. Autistic spectrum disorder and learning disability occurred in more than a third of the examined patients. Considering the hospital-based nature of the sample, these findings may be overestimates. Nevertheless, awareness of this coexistence is important in the diagnosis and habilitation care of children with Mobius sequence. Moreover, the results provide further support for the notion of a subgroup of autistic spectrum disorders being caused by first trimester brain-stem damage.

2.24. Davidovitch, M., Holtzman, G., Tirosh, E. "Autism in the Haifa area—an epidemiological perspective." *Isr Med Assoc J* 2001 Mar;3(3):188-9.

Hannah Khousty Child Development Center, Bnai Zion Medical Center and Rappoport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

BACKGROUND: Autism is a pervasive developmental disorder. The incidence rate and other related epidemiological characteristics of the Israeli population are not available. OBJECTIVES: To assess the incidence rate of autism in the Haifa area and to compare family characteristics with previous reports from other countries. METHODS: We approached facilities in the Haifa area that are involved with the diagnosis and treatment of autism. The study group comprised children born between 1989 and 1993. Records of the children were scrutinized and 69% of the mothers were interviewed. Live-birth cohorts of the same years were employed for incidence computation. RESULTS: An incidence rate of 1/1,000 was derived. Male to female ratio was 4.2:1. Pregnancy and perinatal periods were mostly uneventful. A low prevalence of developmental and emotional morbidity was reported for family members. CONCLUSIONS: The epidemiological characteristics found in the Haifa area are similar to those reported from non-Israeli communities. This finding supports an underlying biological mechanism for this disorder. These data can be used for future trend analyses in Israel.

2.25. Bernard-Opitz, V., Kwook, K.W., Sapuan, S. "Epidemiology of autism in Singapore: findings of the first autism survey." *Int J Rehabil Res* 2001 Mar;24(1):1-6.

Department of Social Work and Psychology, National University of Singapore, Singapore.

The report describes the results of a survey conducted on 176 parents of children with autism in Singapore. The ages of the children ranged from 3 to 12 years. The survey focused on the child's background, behaviour problems and skill profile, the home and school situation as well as the linguistic and social background. It was noted that the Singapore population confirms the international distribution regarding a predominance of boys over girls and a low incidence of birth

complications. A positive trend noted was the fact that 60% of the children were diagnosed before the age of 3 years. Discussion focuses on possible risk factors and psychosocial adversities for autism such as a high frequency of caregivers who are foreign maids, the use of multiple languages and the high level of punitive educational practices. The possible influence of psychosocial deprivation on child development is discussed.

2.26. Dales, L., Hammer, S.J., Smith, N.J. "Time trends in autism and in MMR immunization coverage in California." *JAMA* 2001 Mar 7;285(9):1183-5.

Immunization Branch, California Department of Health Services, 2151 Berkeley Way, Room 712, Berkeley, CA 94704, USA. ldales@dhs.ca.gov

CONTEXT: Considerable concern has been generated in the lay and medical communities by a theory that increased measles-mumps-rubella (MMR) immunization among young children may be the cause of an apparent marked increase in autism occurrence. OBJECTIVE: To determine if a correlation exists in secular trends of MMR immunization coverage among young children and autism occurrence. DESIGN, SETTING, AND PARTICIPANTS: Retrospective analyses of MMR immunization coverage rates among children born in 1980-1994 who were enrolled in California kindergartens (survey samples of 600-1900 children each year) and whose school immunization records were reviewed to retrospectively determine the age at which they first received MMR immunization; and of autism caseloads among children born in these years who were diagnosed with autism and were enrolled in the California Department of Developmental Services regional service center system. MAIN OUTCOME MEASURES: Measles-mumps-rubella immunization coverage rates as of ages 17 months and 24 months and numbers of Department of Developmental Services system enrollees diagnosed with autism, grouped by year of birth. RESULTS: Essentially no correlation was observed between the secular trend of early childhood MMR immunization rates in California and the secular trend in numbers of children with autism enrolled in California's regional service center system. For the 1980-1994 birth cohorts, a marked, sustained increase in autism case numbers was noted, from 44 cases per 100 000 live births in the 1980 cohort to 208 cases per 100 000 live births in the 1994 cohort (a 373% relative increase), but changes in early childhood MMR immunization coverage over the same time period were much smaller and of shorter duration. Immunization coverage by the age of 24 months increased from 72% to 82%, a relative increase of only 14%, over the same time period. CONCLUSIONS: These data do not suggest an association between MMR immunization among young children and an increase in autism occurrence.

2.27. Petrovic, M., Roberts, R., Ramsay, M. "Second dose of measles, mumps, and rubella vaccine: questionnaire survey of health professionals." *BMJ* 2001 Jan 13;322(7278):82-85.

Department of Public Health, North Wales Health Authority, Preswylfa, Mold, Flintshire CH7 1PZ, UK. marko.petrovic@m-wales-ha.wales.nhs.uk

OBJECTIVE: To determine the knowledge, attitudes, and practices among health professionals regarding the measles, mumps, and rubella (MMR) vaccine, particularly the second dose. DESIGN: Self administered postal questionnaire survey. SETTING: North Wales Health Authority, 1998. Participants: 148 health visitors, 239 practice nurses, and 206 general practitioners. MAIN OUTCOME MEASURES: Respondents' views on MMR vaccination, including their views on the likelihood of an association with autism and Crohn's disease and on who is the best person to give advice to parents, whether they agree with the policy of a second dose of the vaccine, and how confident they are in explaining the rationale behind the second dose. RESULTS: Concerning the second dose of the vaccine, 48% of the professionals (220/460) had reservations and 3% (15) disagreed with the policy of giving it. Over half the professionals nominated health visitors as the best initial source of advice on the second vaccine. 61% of health visitors (86/140), compared with 46% of general practitioners (73/158), reported feeling very confident about explaining the rationale of a two dose schedule to a well informed parent, but only 20% (28/138) would unequivocally recommend the second dose to a wavering parent. 33% of the practice nurses (54/163) stated that the MMR vaccine was very likely or possibly associated with Crohn's disease and 27% (44/164) that it was associated with autism. Nearly a fifth of general practitioners (27/158) reported that they had not read the MMR section in the "green book," and 29% (44/152) reported that they had not received the Health Education Authority's factsheet on MMR immunisation. CONCLUSIONS: Knowledge and practice among health professionals regarding the second dose of the MMR vaccine vary widely. Many professionals are not aware of or do not use the good written resources that exist, though local educational initiatives could remedy this.

2.28. Aylott, J. "Autism in adulthood: the concepts of identity and difference." *Br J Nurs* 2000 Jul 13-26;9(13):851-8. Publication Types: Review, Review, Tutorial. Sheffield Hallam University.

It was not until 1980 that autistic spectrum disorders were officially recognized as disorders of development and not of psychoses (Wing, 1996). (In this article the term 'autism' will be used to refer to all individuals diagnosed across the autistic spectrum, including people with Asperger syndrome.) There will be many adults with autism aged over 20 years of age who are not appropriately diagnosed and who are not receiving relevant care (Trevvarthen et al, 1998). Many will have been the victims of a medical model of treatment as opposed to receiving the necessary education and support. This article, the second of a two-part series (the first article (Vol 9(12): 779-84) dealt with children with autism) will explore how contemporary knowledge can help healthcare professionals to support adults with autism in the development of positive self-identities.

2.29. Gillberg, C., Billstedt, E. "Autism and Asperger syndrome: coexistence with other clinical disorders." *Acta Psychiatr Scand* 2000 Nov;102(5):321-30. Publication Types: Review, Review, Tutorial.

Department of Child and Adolescent Psychiatry, University of Goteborg, Sweden.

OBJECTIVE: To provide a clinically useful analysis of the extent to which autism and Asperger syndrome coexist with other disorders. **METHOD:** Selective review of the literature detailing data pertaining to symptoms and disorders sometimes encountered in connection with autism or Asperger syndrome. **RESULTS:** A large number of medical conditions, psychiatric disorders and behavioural and motor dyscontrol symptoms are associated with autism and Asperger syndrome. **CONCLUSION:** Comorbidity is to be expected in autism spectrum disorders -directly or indirectly. Comorbid conditions may be markers for underlying pathophysiology and suggest a more varied treatment approach. There is a great need for in-depth research into this area, meaning that the exclusion criteria of current diagnostic manuals, i.e. those that rule out a diagnosis of autism in some disorders, and a diagnosis of certain other disorders in autism may have to be revised.

2.30. Powell, J.E., Edwards, A., Edwards, M., Pandit, B.S., Sungum-Paliwal, S.R., Whitehouse, W. "Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK." *Dev Med Child Neurol* 2000 Sep;42(9):624-8.

Department of Public Health and Epidemiology, University of Birmingham, UK. J.E.Powell@bham.ac.uk

The incidence of childhood autism and other autistic spectrum disorders (ASDs) in preschool children was determined for two areas of the West Midlands between 1991 and 1996. Children diagnosed before the age of 5 years and residing within the study areas at diagnosis were detected from the records of four child development centres. The incidence rate per 10,000 children per year for the combined areas was 8.3 for all children with ASDs, 3.5 for classical childhood autism (CA), and 4.8 for other ASDs. Rates were similar in both areas, despite differences in social deprivation and proportions of ethnic minorities. While rates for classical CA increased by 18% per year, a much larger increase (55% per year) was seen for 'other ASDs', suggesting that clinicians are becoming increasingly able and/or willing to diagnose ASDs in preschool children.

2.31. Burd, L., Kerbeshian, J., Klug, M.G., McCulloch, K. "A prevalence methodology for mental illness and developmental disorders in rural and frontier settings." *Int J Circumpolar Health* 2000 Jan;59(1):74-86.

Department of Pediatrics and Neuroscience, University of North Dakota School of Medicine, USA.

A prevalence study methodology developed for use in rural and frontier settings is described. The general method was developed over a 15 year period and has been successfully adapted and used in studies of 14 different childhood onset developmental disorders. Subjects were the 168,000 school aged children from North Dakota who were first surveyed for cases of autism—pervasive developmental disorders in 1985 and 1986. The results of the prevalence study were

compared with the results of a 12-year ongoing surveillance of the cohort. The 12-year ongoing surveillance identified one case missed by the original prevalence study. Thus the original prevalence study methodology identified 98% of the cases of autism-pervasive developmental disorder in the population. This methodology may also be useful for studies of other developmental disorders in rural and frontier settings.

2.32. Bower, C., Leonard, H., Petterson, B. "Intellectual disability in Western Australia." *J Paediatr Child Health* 2000 Jun;36(3):213-5.

Division of Epidemiology, TVW Telethon Institute for Child Health Research, West Perth, Disability Services Commission, West Perth, Western Australia, Australia. carolb@ichr.uwa.edu.au

OBJECTIVE: To investigate the prevalence of intellectual disability in Western Australia (WA), its causes, prevention, and trends over time. **METHODOLOGY:** Data from an administrative database of intellectual disability in WA were used to report on the trends in intellectual disability in childhood. **RESULTS:** The prevalence of intellectual disability was 8.3 per 1000 live births in 1980-90. For half the cases, there was no known cause for the intellectual disability. Down syndrome accounted for 14 to 15% of all cases. Since the introduction of newborn screening, no WA-born child participating in the screening program has been diagnosed with intellectual disability as a result of either phenylketonuria or congenital hypothyroidism. The rate of autism spectrum disorders rose from three to six per 10 000 in the 1980-83 WA birth cohort to 10-13 per 10 000 for the 1989-92 cohort. **CONCLUSIONS:** Recent linkage of this administrative database to the WA Maternal and Child Health Research Data Base provides a unique opportunity for more detailed investigation of intellectual disability and its risk factors in a large, well-ascertained population of children.

2.33. Dykens, E.M. "Psychopathology in children with intellectual disability." *J Child Psychol Psychiatry* 2000 May;41(4):407-17. Publication Types: Review, Review, Tutorial.

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Recent advances are reviewed in understanding the heightened prevalence of psychopathology and maladaptive behavior among children with intellectual disability. Researchers have traditionally emphasized measurement and prevalence issues, using either psychiatric assessments or rating scales to identify the prevalence of various problems in children with intellectual disability. Yet the time is ripe to shift directions, and identify more precisely why children are at increased risk for psychopathology to begin with. Although several "biopsychosocial" hypotheses are reviewed, a particularly promising line of work links psychopathology to genetic intellectual disability syndromes. Psychiatric vulnerabilities in several syndromes are reviewed, as are the advantages of phenotypic work for understanding psychopathology among children with intellectual disability more generally.

2.34. Hillman, R.E., Kanafani, N., Takahashi, T.N., Miles, J.H. "Prevalence of autism in Missouri: changing trends and the effect of a comprehensive state autism project." *Mo Med* 2000 May;97(5):159-63.

Department of Child Health, University of Missouri-Columbia.

To assess change in autism prevalence in Missouri from 1988 until 1995, computerized client registries from the Regional Diagnostic Centers were analyzed. In the five to nine year age group, the prevalence rose thirty fold from 0.15 to 4.8 per 10,000. The study period coincides with the establishment of the Missouri Autism Project suggesting that provision of services will increase the apparent prevalence figures and that autistic disorders were previously underdiagnosed in Missouri.

2.35. Kadesjo, B., Gillberg, C. "Tourette's disorder: epidemiology and comorbidity in primary school children." *J Am Acad Child Adolesc Psychiatry* 2000 May;39(5):548-55.

Department of Child and Adolescent Psychiatry, University of Goteborg, Sweden.

OBJECTIVE: To study prevalence and comorbidity of Tourette's disorder in the general population of children and in a clinical setting. **METHODS:** School-age children in the general population and children attending a county-wide tic disorder clinic were screened and examined by the same doctor. Behavioral-psychometric instruments with demonstrated reliability and validity were used. **RESULTS:** Depending on the sample characteristics, 0.15% to 1.1% of all children had Tourette's disorder. Boys outnumbered girls by 4:1 through 6:1. Attention deficits and empathy/autism spectrum problems (including Asperger's disorder) were very common, each type of comorbidity affecting approximately two thirds of individuals with Tourette's disorder. Overall behavior problem scores were high, and affected children exhibited a marked degree of functional impairment. **CONCLUSIONS:** Tourette's disorder is a common disorder with high rates of significant comorbidity. In most cases, attention deficits and empathy problems are likely to cause more suffering than the tics per se.

2.36. Bonde, E. "Comorbidity and subgroups in childhood autism." *Eur Child Adolesc Psychiatry* 2000 Mar;9(1):7-10.

The objective of this study was to identify clinical subgroups in children with childhood autism and to examine comorbidity in each subgroup. The study was based on medical records of 30 inpatients referred to a specialist ward for children with pervasive developmental disorders. Eighteen consecutive patients with an IQ above 50 and fulfilling research criteria for childhood autism were grouped in accordance with the Wing's social subgroups of autism (aloof, passive, and active but odd). Comorbidity, in terms of deficits in attention, motor control, visuo-motor and visuo-spatial function, as well as epilepsy, was described in each of the three groups. The aloof and passive groups produced a pure autistic triad of deficits, while the active but odd group was characterized by strong comorbidity.

2.37. Rosenhall, U., Nordin, V., Sandstrom, M., Ahlsen, G., Gillberg, C. "Autism and hearing loss." *J Autism Dev Disord* 1999 Oct;29(5):349-57.

Department of Audiology, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden. uro@ent.ks.se

A group of 199 children and adolescents (153 boys, 46 girls) with autistic disorder was audiologicaly evaluated. Mild to moderate hearing loss was diagnosed in 7.9% and unilateral hearing loss in 1.6% of those who could be tested appropriately. Pronounced to profound bilateral hearing loss or deafness was diagnosed in 3.5% of all cases, representing a prevalence considerably above that in the general population and comparable to the prevalence found in populations with mental retardation. Hearing deficits in autism occurred at similar rates at all levels of intellectual functioning, so it does not appear that the covariation with intellectual impairment per se can account for all of the variance of hearing deficit in autism. Hyperacusis was common, affecting 18.0% of the autism group and 0% in an age-matched nonautism comparison group. In addition, the rate of serous otitis media (23.5%) and related conductive hearing loss (18.3%) appeared to be increased in autistic disorder. The study emphasizes the need for auditory evaluation of individuals with autism in order to refer those with pronounced to profound hearing loss for aural habilitation and to follow those with mild to moderate hearing loss because of the risk of deterioration.

2.38. Seri, S., Cerquiglini, A., Pisani, F., Curatolo, P. "Autism in tuberous sclerosis: evoked potential evidence for a deficit in auditory sensory processing." *Clin Neurophysiol* 1999 Oct;110(10):1825-30.

Department of Clinical Neurophysiology, The Birmingham Children's Hospital NHS Trust, and The University of Birmingham, UK. stefano.seri@bhamchildrens.wmids.nhs.uk

OBJECTIVE: Autism is a frequent manifestation of tuberous sclerosis complex (TSC) being reported in up to 60% of the patients. Its presence is in association with cortical and subcortical lesions involving the temporal lobes. This study was designed to shed light on the functional mechanisms linking anatomical lesions of TSC and behavioural phenotype by investigating scalp recorded event related potentials to auditory stimuli. **METHODS:** Fourteen children with TSC, seven of which fulfilled the DSM IV criteria for autistic disorder were selected for this study. All of the subjects underwent high resolution MRI, EEG, brainstem auditory evoked potentials, cognitive and behavioural evaluation. Electrical evoked responses to two different pitches, presented with different probability (80% 1000 Hz, 20% 1500 Hz) were recorded from 21 scalp electrodes in the autistic and non-autistic subgroups, to assess central auditory processing and automatic memory. **RESULTS:** The first component of the long latency auditory response (N1) had a significantly prolonged latency with lower amplitude in all of the patients with autistic behaviour who, contrary to non-autistics had MRI lesions involving one or both temporal lobes. A mismatch negativity was detected in all subjects and had a longer latency in subjects with autistic behaviour. **CONCLUSIONS:** To our knowledge

this is the first electrophysiological evidence of a deficit in auditory information processing and automatic memory in TSC patients with autistic behaviour.

2.39. Fombonne, E. "The epidemiology of autism: a review." *Psychol Med* 1999 Jul;29(4):769-86. Publication Types: Review, Review, Tutorial.

MRC Child Psychiatry Unit, Institute of Psychiatry, London.

BACKGROUND: There is some uncertainty about the rate and correlates of autism. **METHOD:** Twenty-three epidemiological surveys of autism published in the English language between 1966 and 1998 were reviewed. **RESULTS:** Over 4 million subjects were surveyed; 1533 subjects with autism were identified. The methodological characteristics of each study are summarized, including case definition, case-finding procedures, participation rates and precision achieved. Across surveys, the median prevalence estimate was 5.2/10000. Half the surveys had 95% confidence intervals consistent with population estimates of 5.4-5.5/10000. Prevalence rates significantly increased with publication year, reflecting changes in case definition and improved recognition; the median rate was 7.2/10 000 for 11 surveys conducted since 1989. The average male/female ratio was 3.8:1, varying according to the absence or presence of mental retardation. Intellectual functioning within the normal range was reported in about 20% of subjects. On average, medical conditions of potential causal significance were found in 6% of subjects with autism, with tuberous sclerosis having a consistently strong association with autism. Social class and immigrant status did not appear to be associated with autism. There was no evidence for a secular increase in the incidence of autism. In eight surveys, rates for other forms of pervasive developmental disorders were two to three times higher than the rate for autism. **CONCLUSION:** Based on recent surveys, a minimum estimate of 18.7/10000 for all forms of pervasive developmental disorders was derived, which outlines the needs in special services for a large group of children.

2.40. Gillberg, C., Wing, L. "Autism: not an extremely rare disorder." *Acta Psychiatr Scand* 1999 Jun;99(6):399-406. Publication Types: Review, Review, Tutorial.

Department of Child and Adolescent Psychiatry, University of Goteborg, Sweden.

OBJECTIVE: To study autism over time in order to ascertain whether there has been an increase in its prevalence in recent years. **METHOD:** All English language papers on the prevalence of autism were reviewed. Ten of the studies retrieved were not used in the final analysis because they did not meet full criteria for inclusion in the review. The remaining 20 studies, published between 1966 and 1997, were subdivided into US studies (n=2) and non-US studies (n=18), and the latter group was subdivided into four 8-year periods. **RESULTS:** The early studies yielded prevalence rates of under 0.5 in 1000 children, whereas the later ones showed a mean rate of about 1 in 1000. There was a marked difference in prevalence rates between those studies that included some children born before 1970 (low rates) and those that included only children born in

1970 and after (high rates). This is probably due to the lower rates obtained by use of criteria strictly based on Kanner's description of his syndrome. The US studies reported atypically low rates. There was a highly significant estimated increase with calendar year in the non-US studies (3.8% per year). **CONCLUSION:** It is concluded that autism is considerably more common than was previously believed. The possible reasons for the higher reported rates are discussed.

2.41. Matsuishi, T., Yamashita, Y., Ohtani, Y., Ornitz, E., Kuriya, N., Murakami, Y., Fukuda, S., Hashimoto, T., Yamashita, F. "Brief report: incidence of and risk factors for autistic disorder in neonatal intensive care unit survivors." *J Autism Dev Disord* 1999 Apr;29(2):161-6.

Department of Pediatrics and Child Health, Kurume University School of Medicine, Japan. tmatsu@med.kurume-u.ac.jp

We investigated prospectively the incidence of autistic disorder (AD) in the neonatal intensive care unit and the risk factors associated with autistic development. The study population included the 5,271 children at St. Mary's Hospital and the diagnosis of AD was performed using DSM-III-R criteria. A total of 36 prenatal, perinatal, and postnatal factors were evaluated in the patients with AD, 57 cerebral palsy (CP), and 214 controls. AD was identified in 18 of the 5,271 children and the incidence was 34 per 10,000 (0.34%). This value was more than twice the highest prevalence value previously reported in Japan. Children with AD had a significantly higher history of the meconium aspiration syndrome ($p = .0010$) than the controls. Autistic patients had different risk factors than CP.

2.42. Fernell, E., Olsson, V.A., Karlgren-Leitner, C., Norlin, B., Hagberg, B., Gillberg, C. "Autistic disorders in children with CHARGE association." *Dev Med Child Neurol* 1999 Apr;41(4):270-2.

Department of Paediatrics, Huddinge University Hospital, Sweden.

Three children with CHARGE association (coloboma, heart defect, atresia of the choanae, retarded growth and development, genital hypoplasia, ear anomalies and hearing defects) as well as concomitant autistic disorder are reported. Two of the children also had mental retardation. Several types of cerebral maldevelopment/dysfunction have been reported in CHARGE association. With regard to aetiology, involvement of the neural crest has been suggested. Autism in CHARGE association may represent a neuro-endocrine dysfunction. Children with a CHARGE association have many medical problems and therefore autistic behaviour can easily be overlooked. A multidisciplinary approach with respect to assessment, treatment, and habilitation is of vital importance.

2.43. Kent, L., Evans, J., Paul, M., Sharp, M. "Comorbidity of autistic spectrum disorders in children with Down syndrome." *Dev Med Child Neurol* 1999 Mar;41(3):153-8.

Parkview Clinic, Moseley, Birmingham, UK.

The aim of the study was to identify the comorbidity of autistic spectrum disorders in a population of children with Down syndrome (DS). All children with DS within a defined population of South Birmingham were identified. The Asperger Syndrome Screening Questionnaire and the Child Autism Rating Scale were completed and diagnosis made according to ICD-10 criteria following interview and observation. Thirty-three of 58 identified children completed the measures, four of whom received a diagnosis of an autistic spectrum disorder. This is equivalent to a minimum comorbid rate of 7%. The questionnaire items concerning social withdrawal, restricted or repetitive interests, clumsiness, and unusual eye contact were associated with an autistic disorder. Of the remaining 29 participating children, 11 also displayed marked obsessional and ritualistic behaviours. The comorbid occurrence of autism and DS is at least 7%. It is important that these children are identified and receive appropriate education and support. A full assessment of social, language, and communication skills and behaviour is crucial, particularly in children with DS who appear different from other children with DS. Potential mechanisms accounting for this comorbidity are discussed.

2.44. Baron-Cohen, S., Mortimore, C., Moriarty, J., Izaguirre, J., Robertson, M. "The prevalence of Gilles de la Tourette's syndrome in children and adolescents with autism." *J Child Psychol Psychiatry* 1999 Feb;40(2):213-8.

Department of Experimental Psychology, University of Cambridge, UK.

Thirty-seven pupils attending a special school for children and adolescents with autism were observed for the presence of motor and vocal tics. Subsequent family interviews confirmed the diagnosis of comorbid Gilles de la Tourette's Syndrome (GTS) in three children with autism, giving a minimum prevalence rate of 8.1%. Family history data also suggested this was heritable. The presence of GTS was not associated with superior intellectual, language, or social development. Results suggest that the rate of GTS in autism may exceed that expected by chance. The limited sample size constrains this conclusion. A large-scale epidemiological study testing this association study would appear merited.

2.45. Hobson, R.P., Lee, A., Brown, R. "Autism and congenital blindness." *J Autism Dev Disord* 1999 Feb;29(1):45-56. Publication Types: Clinical Trial.

Developmental Psychopathology Research Unit, Tavistock Clinic, London, England.

The nature of autism in congenitally blind children has long been a source of interest and perplexity. A group of nine congenitally blind children with an autism-like syndrome were closely matched on chronological age and verbal mental age with nine sighted autistic children, and were compared on the Childhood Autism Rating Scale (Schopler, Reichler, & Renner, 1986) and the Behavior Checklist for Disordered Preschoolers, together with the Play Items for Disordered Preschoolers (Sherman, Shapiro, & Glassman, 1983). A

checklist of clinical features characteristic of autism (derived from DSM-III-R) was also completed through an interview with teachers. There was substantial similarity between the groups, but also suggestive evidence of possible group differences, specifically in the domain of social-emotional responsiveness. Research on the psychological development of congenitally blind children promises to yield insights into the nature of autism itself.

2.46. Barak, Y., Kimhi, R., Stein, D., Gutman, J., Weizman, A. "Autistic subjects with comorbid epilepsy: a possible association with viral infections." *Child Psychiatry Hum Dev* 1999 Spring;29(3):245-51.

Abarbanel Mental Health Center, Bat-Yam, Israel.

This study evaluates the comorbidity of epilepsy as a variable supporting a viral hypothesis in Autism. Data covering a 30-year period (1960-1989), including general population live births, autistic births, and incidence of viral encephalitis and viral meningitis, were collected for Israel. 290 autistic births were evaluated. The annual birth pattern of subjects with comorbid epilepsy fit the seasonality of viral meningitis. These findings support the role of viral C.N.S. infections in the causality of this disorder.

2.47. Mouridsen, S.E., Rich, B., Isager, T. "Epilepsy in disintegrative psychosis and infantile autism: a long-term validation study." *Dev Med Child Neurol* 1999 Feb;41(2):110-4.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

This study aimed to investigate the validity of disintegrative psychosis (DP) as defined in the ICD-9. The history of epilepsy in 13 subjects with DP was compared with that of 39 subjects with infantile autism (IA) who were matched for sex, age, IQ, and socioeconomic status (SES). The average follow-up time was 22 and 23 years (range 11 to 33 years). A significant difference was found between the DP and IA groups in terms of incidence of epilepsy, 77% versus 33% respectively. The peak period of onset of epilepsy occurred before puberty in both groups. Different types of epilepsy were seen, but the psychomotor variant accounted for 50% in the DP group, while 46% of the IA group had the psychomotor and 62% had the grand mal variant. The types are not mutually exclusive. Individuals without epilepsy had significantly higher IQ scores than those with epilepsy, but only within the IA group. The increased risk of developing epilepsy in the DP group is most likely a reflection of an underlying early brain pathology probably present in most individuals with DP. On the whole our findings can be seen as a contribution to the validation of DP as separate from IA, as these two conditions could be distinguished in terms of the way they develop with reference to epilepsy.

2.48. Ho, P.T., Keller, J.L., Berg, A.L., Cargan, A.L., Haddad, J. Jr. "Pervasive developmental delay in children presenting as possible hearing loss." *Laryngoscope* 1999 Jan;109(1):129-35.

Department of Pediatric Otolaryngology, Columbia-Presbyterian Medical Center, Babies and Children's Hospital of New York, New York 10032-3784, USA.

OBJECTIVE/HYPOTHESIS: Children who fail to develop adequate language skills and/or appropriate social skills by age 2 years often are referred to the department of otolaryngology for otolaryngologic examination and evaluation of possible hearing deficits. Discovering a gross disparity between hearing function and language ability often uncovers an underlying developmental disorder satisfying criteria for diagnosis on the spectrum of autism and pervasive developmental delay (PDD). The otolaryngologist has a unique opportunity to identify these autistic children and initiate their evaluation and management. **STUDY DESIGN:** Retrospective review. **METHODS:** Review of charts of children referred over the past 4 years to the Department of Otolaryngology for possible hearing loss identified 15 children who were later diagnosed with PDD. **RESULTS:** Fifteen children initially referred for hearing evaluation were subsequently identified with a diagnosis of PDD. Males outnumbered females 4 to 1, with the average age of referral being 2 years. One third of the patients displayed middle ear disease that improved with PE tube placement. One third of the patients showed brainstem conduction dysfunction on auditory brainstem evoked response testing. **CONCLUSIONS:** Children with developmental delays, especially higher functioning ones, may present with a myriad of language and communication deficits that are often mistakenly attributed to hearing loss. Otolaryngologists and audiologists can assist in their early identification and appropriate referral for therapy.

2.49. Shavelle, R.M., Strauss, D. "Comparative mortality of persons with autism in California, 1980-1996." *J Insur Med* 1998;30(4):220-5.

Department of Statistics, University of California, Riverside 92521-0138, USA.

The authors studied mortality rates of persons with autism, using the extensive California developmental disabilities registry. There was an overall mortality ratio (MR) of 213%. The MR for females (490%) was strikingly higher than for males (167%). The excess mortality rate (EDR) increased with age, while the mortality ratio (MR) decreased with age. Persons with autism are subject to increased mortality risk, as summarized in the provided tables.

2.50. Bailey, D.B. Jr, Mesibov, G.B., Hatton, D.D., Clark, R.D., Roberts, J.E., Mayhew, L. "Autistic behavior in young boys with fragile X syndrome." *J Autism Dev Disord* 1998 Dec;28(6):499-508.

University of North Carolina at Chapel Hill 27599, USA.

A sample of 57 boys with fragile X syndrome (fraX) between the ages of 24 and 133 months was rated using the Childhood Autism Rating Scale (CARS) to assess the extent to which autism and autistic features were evident in a young population. Fourteen subjects (approximately 25% of the

sample) scored above the cutoff for autism, suggesting a relatively high incidence of autistic behavior. All but 2 of these 14 were in the mildly or moderately autistic range, however, and only a few items received severe ratings, suggesting that severe autism is relatively rare in fraX, at least during the early years. The CARS resulted in a continuum of autistic ratings in the fraX population, but no particular items on the CARS contributed disproportionately to autism ratings. A visual comparison of ratings on an autistic, non-fraX sample revealed similar profiles of ratings, suggesting that differentiating fraX and autism on the basis of CARS ratings is not likely. Within the fraX group, chronological age and socioeconomic status did not correlate with CARS ratings, but severity of delay was strongly related, such that more severely delayed children scored higher (more autistic) on the CARS.

2.51. Zappella, M., Gillberg, C., Ehlers, S. "The preserved speech variant: a subgroup of the Rett complex: a clinical report of 30 cases." *J Autism Dev Disord* 1998 Dec;28(6):519-26.

Department of Child Neuropsychiatry, General Hospital of Siena, Italy.

Thirty girls and young women, 6 from Sweden and 24 from Italy, are described in this paper. They ranged in age from 5 through 28 years. All but one of the cases met full symptom criteria for DSM-IV autistic disorder. However, they also showed many features of classic Rett syndrome (RS) as outlined by the Rett syndrome Diagnostic Criteria Work Group. All met the required 3 out of 6 main criteria and 47% also met both these and the required 5 out of 11 supportive criteria for RS variants as outlined by Hagberg. The course of the disorder was more benign than in classic RS, but all the girls were severely functionally impaired. There was familial clustering in a subgroup. It is concluded that these 30 cases represent a syndrome, similar and probably related, to classic RS. It is suggested that there is a spectrum of syndromes ranging from severe cases with classical presentation to considerably milder variants. We propose that, at the present state of knowledge, these conditions might be best categorized as subgroups of the "Rett Complex," in which classical RS and the preserved speech variant may be the most frequent.

2.52. Kobayashi, R., Murata, T. "Setback phenomenon in autism and long-term prognosis." *Acta Psychiatr Scand* 1998 Oct;98(4):296-303.

Department of Social Work, Tokai University School of Health Sciences, Kanagawa, Japan.

From among the subjects of a follow-up study on cases of autism conducted by the authors in 1990, 179 cases for which precise records were available on the infancy period were selected for evaluation of the relationship between the occurrence of setback phenomenon in infancy and long-term prognosis. The following results were obtained: (i) a significantly higher rate of epilepsy among the setback group compared to the non-setback group; and (ii) a significantly lower level of language development among the setback group

upon entering elementary school compared to the non-setback group, although the difference between the present levels of adaptation of the two groups was not significant. Factors determining the long-term prognosis of the setback group are discussed.

2.53. Feinstein, C., Reiss, A.L. "Autism: the point of view from fragile X studies." *J Autism Dev Disord* 1998 Oct;28(5):393-405. Publication Types: Review, Review, Tutorial.

Division of Child and Adolescent Psychiatry and Child Development, Stanford University School of Medicine, California 94305-5719, USA.

The relationship between the fragile X syndrome (FXS) and autism is reviewed. Shortly after the FXS was first described, it was noted that certain behaviors commonly found in afflicted individuals resemble certain features of autism. Research concerning a possible relationship between these conditions is summarized. The outcome of this research indicates that FXS is not a common cause of autism, although the number of individuals with FXS who meet diagnostic criteria for autism is higher than can be accounted for by chance. The major focus of this paper highlights that FXS is a well-defined neurogenetic disease that includes a cognitive behavioral phenotype, and has both a known biological cause and an increasing well-delineated pathogenesis. Autism is a behaviorally defined syndrome whose syndromic boundaries

and biological causes are not known. These profound differences complicate comparisons and causal discussions. However, the behavioral neurogenetic information available about FXS suggests certain pathways for future research directed at elucidating the syndrome of autism.

2.54. Prochner, L. "The development of the day treatment centre for emotionally disturbed children at the West End Creche, Toronto." *Bull Can Hist Med* 1997; 14(2) : 2154-39. Publication Types:Historical Article.

Education Department, Concordia University, Montreal, Quebec.

This article describes the interplay of various interests in centre-based child care from the 1930s to the late 1960s through an examination of the development of a treatment centre for children with autism at the West End Creche in Toronto. The impact of the attention to child care during World War II in North America is described in relation to the postwar trend to reorient child care away from a service for wage-earning mothers and towards an educational-therapeutic service for children and families. The role of local and international welfare associations, as well as the influence of the interrelated professions of child psychiatry, social work, and nursery education, is reviewed. Finally, implications for current developments in the field of early childhood education are discussed.

MANIFESTATION

Neuro Psychological

3.1.1. Perez-Jimenez, A., Villarejo, F.J., Fournier del Castillo, M.C., Garcia-Penas, J.J., Carreno, M. "Continuous giggling and autistic disorder associated with hypothalamic hamartoma." *Epileptic Disord.* 2003 Mar;5(1):31-7.

Clinical Neurophysiology section, Nino Jesus University Hospital, Madrid, Spain. mperez.hnjs@salud.madrid.org

We present the case of a child affected since early infancy from recurring episodes of giggling mixed with stereotypical behaviours, mingled with head drops, and eventually with falls, in the context of an autistic disorder. Scalp video-EEG recordings revealed an epileptic encephalopathy with generalized slow spike-and-wave complexes alternating with electrodecremental periods, which generally corresponded to the onset of the aforementioned clinical sequences. A resection of a hypothalamic hamartoma was achieved at the age of two. Since then, after 22 months of follow-up, the child is totally free from the giggling and the drops, and the autistic behaviour significantly improved during the second year of follow-up. This case illustrates the difficulties to recognize some subtle ictal manifestations during infancy and childhood, and encourages the early surgical treatment of hypothalamic hamartomas when associated with epileptic encephalopathy and when technically possible.

3.1.2. Askalan, R., Mackay, M., Brian, J., Otsubo, H., McDermott, C., Bryson, S., Boyd, J., Snead, C. 3rd, Roberts, W., Weiss, S. "Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms." *J Child Neurol.* 2003 Mar;18(3):165-70. Publication Types: Clinical Trial.

Division of Neurology, The Hospital for Sick Children, Toronto ON, Canada.

The objective of this study was to compare the efficacy of corticotropin (ACTH) versus vigabatrin in treating infantile spasms and to determine which medication has a more favorable long-term outcome in terms of cognitive function, evolution of epilepsy, and incidence of autism. Patients with infantile spasms were included in the study if they were 3 to 16 months old, had hypsarrhythmia, and had no previous treatment with vigabatrin or corticosteroids. Patient evaluation included electroencephalographic and psychometric measures before and after treatment. Patients were stratified based on etiology (idiopathic or symptomatic) and sex and then randomized between the ACTH and vigabatrin treatment groups. Each of the treatment groups received either ACTH or vigabatrin for 2 weeks. At the end of 2 weeks of treatment, patients were considered responders if spasms and hypsarrhythmia resolved. Nonresponders were crossed over and treated with the alternate drug. Nine patients were included in the study. Three patients received ACTH, one of whom was a responder. Six patients received vigabatrin, three of whom were responders. The five nonresponders received both therapies. All patients had some degree of developmental plateau or regression before the initiation of treatment. Four patients with idiopathic infantile spasms showed improved cognitive function following treatment. The remaining five patients remained significantly

delayed. Five patients with symptomatic infantile spasms had epilepsy following treatment; three of them were in the autistic spectrum. The small number of infants in this pilot study is insufficient to determine which of the two drugs is more effective. However, the following trends were identified: vigabatrin may be more effective for patients with symptomatic infantile spasms; patients with idiopathic infantile spasms tend to have a better cognitive outcome; and patients with symptomatic infantile spasms tend to develop both epilepsy and autism.

3.1.3. Cuccaro, M.L., Shao, Y., Bass, M.P., Abramson, R.K., Ravan, S.A., Wright, H.H., Wolpert, C.M., Donnelly, S.L., Pericak-Vance, M.A. "Behavioral comparisons in autistic individuals from multiplex and singleton families." *J Autism Dev Disord.* 2003 Feb;33(1):87-91.

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Autistic disorder (AD) is a complex neurodevelopmental disorder. The role of genetics in AD etiology is well established, and it is postulated that anywhere from 2 to 10 genes could be involved. As part of a larger study to identify these genetic effects we have ascertained a series of AD families: Sporadic (SP, 1 known AD case per family and no known history of AD) and multiplex (MP, > or = 2 cases per family). The underlying etiology of both family types is unknown. It is possible that MP families may constitute a unique subset of families in which the disease phenotype is more likely due to genetic factors. Clinical differences between the two family types could represent underlying genetic heterogeneity. We examined ADI-R data for 69 probands from MP families and 88 from SP families in order to compare and contrast the clinical phenotypes for each group as a function of verbal versus nonverbal status. Multivariate analysis controlling for covariates of age at examination, gender, and race (MANCOVA) revealed no differences between either the verbal or nonverbal MP and SP groups for the three ADI-R area scores: social interaction, communication, and restricted/repetitive interests or behaviors. These data failed to find clinical heterogeneity between MP and SP family types. This supports previous work that indicated that autism features are not useful as tools to index genetic heterogeneity. Thus, although there may be different underlying etiologic mechanisms in the SP and MP probands, there are no distinct behavioral patterns associated with probands from MP families versus SP families. These results suggest the possibility that common etiologic mechanisms, either genetic and/or environmental, could underlie all of AD.

3.1.4. Blake, R., Turner, L.M., Smoski, M.J., Pozdol, S.L., Stone, W.L. "Visual recognition of biological motion is impaired in children with autism." *Psychol Sci.* 2003 Mar;14(2):151-7.

Department of Psychology, Vanderbilt University, Nashville, TN 37201, USA. randolph.blake@vanderbilt.edu

Autistic children and typically developing control children were tested on two visual tasks, one involving grouping of

small line elements into a global figure and the other involving perception of human activity portrayed in point-light animations. Performance of the two groups was equivalent on the figure task, but autistic children were significantly impaired on the biological motion task. This latter deficit may be related to the impaired social skills characteristic of autism, and we speculate that this deficit may implicate abnormalities in brain areas mediating perception of human movement.

3.1.5. Mari, M., Castiello, U., Marks, D., Marraffa, C., Prior, M. "The reach-to-grasp movement in children with autism spectrum disorder." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):393-403. Publication Types: Review, Review Literature.

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Autism is associated with a wide and complex array of neurobehavioural symptoms. Examination of the motor system offers a particularly appealing method for studying autism by providing information about this syndrome that is relatively immune to experimental influence. In this article, we considered the relationship between possible movement disturbance and symptoms of autism and introduced an experimental model that may be useful for rehabilitation and diagnostic purposes: the reach-to-grasp movement. Research is reviewed that characterizes kinematically the reach-to-grasp movement in children with autism compared with age-matched 'controls'. Unlike the age-matched children, autistic children showed differences in movement planning and execution, supporting the view that movement disturbances may play a part in the phenomenon of autism.

3.1.6. Booth, R., Charlton, R., Hughes, C., Happe, F. "Disentangling weak coherence and executive dysfunction: planning drawing in autism and attention-deficit/hyperactivity disorder." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):387-92.

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A tendency to focus on details at the expense of configural information, 'weak coherence', has been proposed as a cognitive style in autism. In the present study we tested whether weak coherence might be the result of executive dysfunction, by testing clinical groups known to show deficits on tests of executive control. Boys with autism spectrum disorders (ASD) were compared with age- and intelligence quotient (IQ)-matched boys with attention-deficit/hyperactivity disorder (ADHD), and typically developing (TD) boys, on a drawing task requiring planning for the inclusion of a new element. Weak coherence was measured through analysis of drawing style. In line with the predictions made, the ASD group was more detail-focused in their drawings than were either ADHD or TD boys. The ASD and ADHD groups both showed planning impairments, which were more severe in the former group. Poor planning did not, however, predict detail-focus, and scores on the two aspects

of the task were unrelated in the clinical groups. These findings indicate that weak coherence may indeed be a cognitive style specific to autism and unrelated to cognitive deficits in frontal functions.

3.1.7. Plaisted, K., Saksida, L., Alcantara, J., Weisblatt, E. "Towards an understanding of the mechanisms of weak central coherence effects: experiments in visual configural learning and auditory perception." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):375-86.

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The weak central coherence hypothesis of Frith is one of the most prominent theories concerning the abnormal performance of individuals with autism on tasks that involve local and global processing. Individuals with autism often outperform matched nonautistic individuals on tasks in which success depends upon processing of local features, and underperform on tasks that require global processing. We review those studies that have been unable to identify the locus of the mechanisms that may be responsible for weak central coherence effects and those that show that local processing is enhanced in autism but not at the expense of global processing. In the light of these studies, we propose that the mechanisms which can give rise to 'weak central coherence' effects may be perceptual. More specifically, we propose that perception operates to enhance the representation of individual perceptual features but that this does not impact adversely on representations that involve integration of features. This proposal was supported in the two experiments we report on configural and feature discrimination learning in high-functioning children with autism. We also examined processes of perception directly, in an auditory filtering task which measured the width of auditory filters in individuals with autism and found that the width of auditory filters in autism were abnormally broad. We consider the implications of these findings for perceptual theories of the mechanisms underpinning weak central coherence effects.

3.1.8. Baron-Cohen, S., Richler, J., Bisarya, D., Gurunathan, N., Wheelwright, S. "The systemizing quotient: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):361-74.

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Systemizing is the drive to analyse systems or construct systems. A recent model of psychological sex differences suggests that this is a major dimension in which the sexes differ, with males being more drawn to systemize than females. Currently, there are no self-report measures to assess this important dimension. A second major dimension of sex differences is empathizing (the drive to identify mental states and respond to these with an appropriate emotion). Previous

studies find females score higher on empathy measures. We report a new self-report questionnaire, the Systemizing Quotient (SQ), for use with adults of normal intelligence. It contains 40 systemizing items and 20 control items. On each systemizing item, a person can score 2, 1 or 0, so the SQ has a maximum score of 80 and a minimum of zero. In Study 1, we measured the SQ of $n = 278$ adults (114 males, 164 females) from a general population, to test for predicted sex differences (male superiority) in systemizing. All subjects were also given the Empathy Quotient (EQ) to test if previous reports of female superiority would be replicated. In Study 2 we employed the SQ and the EQ with $n = 47$ adults (33 males, 14 females) with Asperger syndrome (AS) or high-functioning autism (HFA), who are predicted to be either normal or superior at systemizing, but impaired at empathizing. Their scores were compared with $n = 47$ matched adults from the general population in Study 1. In Study 1, as predicted, normal adult males scored significantly higher than females on the SQ and significantly lower on the EQ. In Study 2, again as predicted, adults with AS/HFA scored significantly higher on the SQ than matched controls, and significantly lower on the EQ than matched controls. The SQ reveals both a sex difference in systemizing in the general population and an unusually strong drive to systemize in AS/HFA. These results are discussed in relation to two linked theories: the 'empathizing-systemizing' (E-S) theory of sex differences and the extreme male brain (EMB) theory of autism.

3.1.9. Swettenham, J., Condie, S., Campbell, R., Milne, E., Coleman, M. "Does the perception of moving eyes trigger reflexive visual orienting in autism?" *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):325-34.

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Does movement of the eyes in one or another direction function as an automatic attentional cue to a location of interest? Two experiments explored the directional movement of the eyes in a full face for speed of detection of an aftercoming location target in young people with autism and in control participants. Our aim was to investigate whether a low-level perceptual impairment underlies the delay in gaze following characteristic of autism. The participants' task was to detect a target appearing on the left or right of the screen either 100 ms or 800 ms after a face cue appeared with eyes averting to the left or right. Despite instructions to ignore eye-movement in the face cue, people with autism and control adolescents were quicker to detect targets that had been preceded by an eye movement cue congruent with target location compared with targets preceded by an incongruent eye movement cue. The attention shifts are thought to be reflexive because the cue was to be ignored, and because the effect was found even when cue-target duration was short (100 ms). Because (experiment two) the effect persisted even when the face was inverted, it would seem that the direction of movement of eyes can provide a powerful (involuntary) cue to a location.

3.1.10. Charman, T. "Why is joint attention a pivotal skill in autism?" *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):315-24.

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Joint attention abilities play a crucial role in the development of autism. Impairments in joint attention are among the earliest signs of the disorder and joint attention skills relate to outcome, both in the 'natural course' of autism and through being targeted in early intervention programmes. In the current study, concurrent and longitudinal associations between joint attention and other social communication abilities measured in a sample of infants with autism and related pervasive developmental disorders at age 20 months, and language and symptom severity at age 42 months, were examined. Extending the findings from previous studies, joint attention ability was positively associated with language gains and (lower) social and communication symptoms, and imitation ability was also positively associated with later language. Some specificity in the association between different aspects of joint attention behaviours and outcome was found: declarative, triadic gaze switching predicted language and symptom severity but imperative, dyadic eye contact behaviours did not. Further, although joint attention was associated with later social and language symptoms it was unrelated to repetitive and stereotyped symptoms, suggesting the latter may have a separate developmental trajectory. Possible deficits in psychological and neurological processes that might underlie the impaired development of joint attention in autism are discussed.

3.1.11. Tager-Flusberg, H., Joseph, R.M. "Identifying neurocognitive phenotypes in autism." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):303-14. Publication Types: Review, Review Literature.

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Autism is a complex disorder that is heterogeneous both in its phenotypic expression and its etiology. The search for genes associated with autism and the neurobiological mechanisms that underlie its behavioural symptoms has been hampered by this heterogeneity. Recent studies indicate that within autism, there may be distinct subgroups that can be defined based on differences in neurocognitive profiles. This paper presents evidence for two kinds of subtypes in autism that are defined on the basis of language profiles and on the basis of cognitive profiles. The implications for genetic and neurobiological studies of these subgroups are discussed, with special reference to evidence relating these cognitive phenotypes to volumetric studies of brain size and organization in autism.

3.1.12. Hill, E.L., Frith, U. "Understanding autism: insights from mind and brain." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):281-9. Publication Types: Review, Review Literature.

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Autism is a developmental disorder characterized by impaired social interaction and communication as well as repetitive behaviours and restricted interests. The consequences of this disorder for everyday life adaptation are extremely variable. The general public is now more aware of the high prevalence of this lifelong disorder, with ca. 0.6% of the population being affected. However, the signs and symptoms of autism are still puzzling. Since a biological basis of autism was accepted, approaches from developmental cognitive neuroscience have been applied to further our understanding of the autism spectrum. The study of the behavioural and underlying cognitive deficits in autism has advanced ahead of the study of the underlying brain abnormalities and of the putative genetic mechanisms. However, advances in these fields are expected as methodological difficulties are overcome. In this paper, recent developments in the field of autism are outlined. In particular, we review the findings of the three main neuro-cognitive theories of autism: theory-of-mind deficit, weak central coherence and executive dysfunction.

3.1.13. Medina, A.C., Sogbe, R., Gomez-Rey, A.M., Mata, M. "Factitial oral lesions in an autistic paediatric patient." *Int J Paediatr Dent.* 2003 Mar;13(2):130-7.

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Self Injurious Behaviour (SIB) is a deliberate harm to the body that may lead to factitial injuries. Its origin may be functional or biological and it has a higher prevalence in females and in psychologically impaired individuals. Seventy per cent of autistic patients have SIB. Seventy-five per cent of factitial injuries are located in the head and neck region. A paediatric case report concerning a 4-year-old autistic female is presented. Detailed medical history, physical examination, clinical intraoral and radiographic examination, incisional biopsy, neuropaediatric, psychological and speech evaluation were undertaken. Diagnosis included hypochromic macrocytic anaemia, caries, coronal fracture, factitial ulcer, factitial periodontitis, self-extraction of primary teeth and permanent teeth buds, non-specific oral ulcer with inflammatory reaction, mild mental retardation, speech impairment, autistic syndrome and self injurious behaviour consisting of putting fingers and foreign objects in the gingiva, fingernail biting and hair pulling. Differential diagnosis included hystiocytosis X, prepuberal periodontitis and leukocyte adhesion deficiency. Dental preventive and restorative treatment was performed. Non-contingent reinforcement therapy was successfully used to diminish SIB. Treatment of factitial oral injuries must be interdisciplinary and requires cooperation of the patient, the parents, health care providers, and medical team.

3.1.14. Lopez, B., Leekam, S.R. "Do children with autism fail to process information in context?" *J Child Psychol Psychiatry.* 2003 Feb;44(2):285-300.

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BACKGROUND: This research investigated the proposal that children with autism are impaired in processing information in its context. To date, this proposal rests almost exclusively on evidence from verbal tasks. Given evidence of visuo-spatial proficiency in autism in other areas of functioning, it is possible that the ability to use context is spared in the visual domain but impaired in the verbal domain. **METHOD:** Fifteen children with autism and 16 age and IQ-matched typically developing children were tested on their ability to take account of visual context information (Experiment 1) and verbal context information (Experiment 2) using an adaptation of Palmer's (1975) visual context task. They were also given an adaptation of Tager-Flusberg's (1991) visual and verbal semantic memory task (Experiment 3) and Frith and Snowling's (1983) homograph task (Experiment 4). **RESULTS:** Experiment 1 showed that children with autism were facilitated by the provision of visual context information. Experiments 2 and 3 showed that the same children were also able to use both verbal context information when identifying words and semantic category information in a verbal task when naming and recalling words. However, in Experiment 4 these children had difficulties with a sentence-processing task when using sentence context to disambiguate homographs. **CONCLUSIONS:** These findings demonstrate that children with autism do not have a general difficulty in connecting context information and item information as predicted by weak central coherence theory. Instead the results suggest that there is specific difficulty with complex verbal stimuli and in particular with using sentence context to disambiguate meaning.

3.1.15. Mann, T.A., Walker, P. "Autism and a deficit in broadening the spread of visual attention." *J Child Psychol Psychiatry.* 2003 Feb;44(2):274-84.

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BACKGROUND: This study examines if visual attention in autism is spatially overfocused (Townsend & Courchesne, 1994) and if there is an associated deficit in broadening the spatial spread of attention. **METHOD:** Two crosshairs were presented on each trial separated by a brief (500 ms) interval. There was a modest difference in the lengths of the two hairs in each crosshair and participants had to decide which one was longest. Previous research (Mack & Rock, 1998) has revealed that in making this judgement people spread their visual attention to embrace the whole crosshair. Varying the overall size of each crosshair was intended to control participants' spread of attention. The impact of the size of the first crosshair gave an indication of participants' default setting for the spread of attention. The impact of the size transition between the first and second crosshair gave an indication of the fluency with which participants could change the spatial spread of visual attention. **RESULTS:** Based on the

first proposal it was predicted that individuals with autism (N = 13), relative to ability-matched moderately learning disabled (N = 15) and typically developing individuals (N = 15), would be more accurate and quicker to respond when the first crosshair was small rather than large. However, the results revealed no effects of the size of the first crosshair and no group differences. Based on the second proposal it was predicted that individuals with autism, relative to both control groups, would be less accurate and slower to respond to the second crosshair when the size transition from the first crosshair involved a change from small to large (in comparison with large to large), but would not differ when the change was from large to small (in comparison with small to small). This prediction was confirmed. **CONCLUSION:** Autism is associated with a deficit in broadening the spatial spread of visual attention. The implications of this for other visual and attentional anomalies observed in autism are discussed.

3.1.16. Spitzer, S.L. "Using participant observation to study the meaning of occupations of young children with autism and other developmental disabilities." *Am J Occup Ther.* 2003 Jan-Feb;57(1):66-76.

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Understanding the individual meaning of daily activities for children with developmental disabilities such as autism is both important and challenging for researchers and practitioners. Rigorous participant observation offers a method for developing this knowledge base by including the child's perspective. Through literature and examples from an ethnography of young children with autism, this article illustrates the application of participant observation to children with developmental disabilities. Specific strategies can promote valid interpretations despite developmental, linguistic, and perceptual differences between adult researchers and child participants.

3.1.17. Planche, P. "Information processing in autistic children: more sequential or more simultaneous?" *Int J Circumpolar Health.* 2002;61 Suppl 2:4-14.

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The objective of this study was to refine the understanding of cognitive troubles in autism and to clarify the modes of information processing mobilized by the subjects. Eight children were examined, aged 4;9-9;1, with a diagnosis of moderate autism. The Kaufman Assessment Battery for Children (K-ABC) was presented to each child. The results support an executive functioning deficit interpretation and a weak drive for central coherence in autism. Practical implications of this study in terms of follow up are also discussed.

3.1.18. Mukaddes, N.M. "Gender identity problems in autistic children." *Child Care Health Dev.* 2002 Nov;28(6):529-32.

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Several psychiatric and behavioural problems have been described in children with autism. The aim of this case report is to discuss the developmental pattern of cross-gender behaviour in children with autistic disorder. Two boys are described with high functioning autism, followed for about 4 years, who showed persistent gender identity problems.

3.1.19. Koczat, D.L., Rogers, S.J., Pennington, B.F., Ross, R.G. "Eye movement abnormality suggestive of a spatial working memory deficit is present in parents of autistic probands." *J Autism Dev Disord.* 2002 Dec;32(6):513-8.

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Autistic probands exhibit impaired spatial accuracy and impaired response suppression errors during a delayed oculomotor response task. Family members of autistic probands, and thus the possible familial nature of these deficits, have not been assessed. Eleven parents of autistic probands and 17 adults from unaffected families, ages 25-50 years, completed oculomotor delayed-response tasks. Parents of autistic probands demonstrated poorer spatial accuracy than the comparison group ($p = .002$), with no significant differences between groups on percentage of premature saccades or latency of remembered saccades. Spatial working memory deficits, as measured by the delayed oculomotor response task, appear to be familial in families with an autistic proband. These deficits deserve further evaluation as a potential endophenotypic marker for genetic risk for autism.

3.1.20. Stahl, L., Pry, R. "Joint attention and set-shifting in young children with autism." *Autism.* 2002 Dec;6(4):383-96.

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Executive function deficits in autism have been consistently found in many studies, using a wide range of measures, but usually involving older children and adults and those of higher IQ. The interpretation of executive function deficits is difficult because the concept itself is poorly defined (inhibition of prepotent responses, set-shifting, action planning etc.). Analyses have focused mainly on the attention participants pay to physical entities (object handling and problem solving) rather than social ones. The present study investigated whether these two types of attention are linked in autistic development. Fifteen children with autism (mean mental age = 24 months) were compared to 21 normally developing children (mean mental age = 25 months). A strong correlation was found between joint attention and set-shifting in the typically developing children but not those with autism. The results are discussed from a psychopathological perspective on development.

3.1.21. Ruble, L.A., Scott, M.M. "Executive functions and the natural habitat behaviors of children with autism." *Autism*. 2002 Dec;6(4):365-81.

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Research suggests that impairments in executive functions play a role in the cognitive deficit in autism. Possible autism-specific impairments include an inability to engage in goal-directed behaviors and adjust behaviors given environmental demands. What has been described as executive functions is based largely on observations of performance in the laboratory rather than in natural settings. An ecological method first described by Barker and Wright and adapted by Scott was used to assess the patterns of goal-directed behaviors of eight children with autism and eight chronological and mental age comparable children with Down syndrome. Quantitative and qualitative features of naturalistic behaviors were collected, and coded using previously described categories of children's behavior. Results indicated that children with autism exhibited shorter and less overlapping goal-directed behaviors. These data suggest a cognitive difference rather than developmental delay, and lend support for impaired executive functions in autism. Practical implications for educators and caregivers are discussed.

3.1.22. Wellman, H.M., Baron-Cohen, S., Caswell, R., Gomez, J.C., Swettenham, J., Toye, E., Lagattuta, K. "Thought-bubbles help children with autism acquire an alternative to a theory of mind." *Autism*. 2002 Dec;6(4):343-63. Publication Types: Clinical Trial.

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Children with autism have specific difficulties understanding complex mental states like thought, belief, and false belief and their effects on behaviour. Such children benefit from focused teaching, where beliefs are likened to photographs-in-the-head. Here two studies, one with seven participants and one with 10, tested a picture-in-the-head strategy for dealing with thoughts and behaviour by teaching children with autism about cartoon thought-bubbles as a device for representing such mental states. This prosthetic device led children with autism to pass not only false belief tests, but also related theory of mind tests. These results confirm earlier findings of the efficacy of picture-in-the-head teaching about mental states, but go further in showing that thought-bubble training more easily extends to children's understanding of thoughts (not just behaviour) and to enhanced performance on several transfer tasks. Thought-bubbles provide a theoretically interesting as well as an especially easy and effective teaching technique.

3.1.23. Militerni, R., Bravaccio, C., Falco, C., Fico, C., Palermo, M.T. "Repetitive behaviors in autistic disorder." *Eur Child Adolesc Psychiatry*. 2002 Oct;11(5):210-8.

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INTRODUCTION: Repetitive behaviors are common in autistic disorder, as in other developmental disabilities. Behaviors as diverse as stereotypies, cognitive inflexibility, and a need for sameness are grouped together under DSM IV classification, even though they are diverse in phenomenology, underlying neural circuitry, and possible clinical significance. In order to better define repetitive behaviors, we studied the relationship between such behaviors and chronological age, developmental level, estimated IQ, presumed mood state, severity of illness, as well as behavior reactivity to environmental stimuli, in a group of 121 consecutive autistic children, aged 2-4 and 7-11 years. RESULTS: Younger autistic children displayed more motor and sensory repetitive behaviors. Older children had more complex behaviors. Children with higher IQ scores, likewise, demonstrated more complex repetitive behaviors. Most motor behaviors and self injury showed features of reactivity. CONCLUSIONS: Certain "repetitive" activities may not represent core features of autistic disorder and may be equivalent to normal motor and cognitive behaviors, as seen during typical development.

3.1.24. Duker, P.C., Douwenga, H., Joosten, S., Franken, T. "Effects of single and repeated shock on perceived pain and startle response in healthy volunteers." *Res Dev Disabil* 2002 Jul-Aug;23(4):285-92

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Contingent shock (CS) has been used in a number of studies to suppress health-threatening self-injurious behavior of individuals with mental retardation and autism. As sustained suppression is an issue of concern, research into procedural variables of CS is needed. In this study, clinical evidence was used to infer a variable that might be of relevance for the application of clinical contingent shock, that is, to assess the effect of single versus repeated shock at a specific location on the body. With pain intensity and startle response as dependent variables, shocks were administered to 48 healthy volunteers. Electric shocks were identical to those that used in clinical practice. The second shock in succession to the same location of the body produced higher pain intensity ratings than the first shock and that the third shock in succession to the same location of the body produced higher pain intensity ratings than the second shock in succession. Startle responses, however, failed to be affected in this direction. The latter result is consistent with a previous study. Our data suggest that repeated shock to the same location is likely to be more effective to establish suppression than repeated shock to different locations.

3.1.25. Lindauer, S.E., Zarcone, J.R., Richman, D.M., Schroeder, S.R. "A comparison of multiple reinforcer assessments to identify the function of maladaptive behavior." *J Appl Behav Anal* 2002 Fall;35(3):299-303

Functional analysis results indicated that maladaptive behaviors displayed by a 25-year-old man with profound mental retardation were maintained by attention from caregivers and possibly, to a lesser degree, by access to tangible items. A concurrent-schedules procedure was then

used to study the relative reinforcing value for maladaptive behavior of attention versus tangible items. Results of the concurrent-schedules assessment and subsequent functional communication training indicated that preference for attention versus access to a tangible object varied.

3.1.26. Peterson, C.C. "Drawing insight from pictures: the development of concepts of false drawing and false belief in children with deafness, normal hearing, and autism." *Child Dev* 2002 Sep-Oct;73(5):1442-59.

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Theory-of-mind concepts in children with deafness, autism, and normal development (N = 154) were examined in three experiments using a set of standard inferential false-belief tasks and matched sets of tasks involving false drawings. Results of all three experiments replicated previously published findings by showing that primary school children with deafness or autism, aged 6 to 13 years, scored significantly lower than normal-developing 4-year-old preschoolers on standard misleading-container and unseen-change tests of false-belief understanding. Furthermore, deaf and autistic children generally scored higher on drawing-based tests than on corresponding standard tests and, on the most challenging of the false-drawing tests in Experiment 2, they significantly outperformed the normal-developing preschoolers by clearly understanding their own false intentions and another person's false beliefs about an actively misleading drawing. In Experiment 3, preschoolers outperformed older deaf and autistic children on standard tasks, but did less well on a task that required the drawing of a false belief. Methodological factors could not fully explain the findings, but early social and conversational experiences in the family were deemed likely contributors.

3.1.27. Klin, A., Jones, W., Schultz, R., Volkmar, F., Cohen, D. "Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism." *Arch Gen Psychiatry* 2002 Sep;59(9):809-16.

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BACKGROUND: Manifestations of core social deficits in autism are more pronounced in everyday settings than in explicit experimental tasks. To bring experimental measures in line with clinical observation, we report a novel method of quantifying atypical strategies of social monitoring in a setting that simulates the demands of daily experience. Enhanced ecological validity was intended to maximize between-group effect sizes and assess the predictive utility of experimental variables relative to outcome measures of social competence. **METHODS:** While viewing social scenes, eye-tracking technology measured visual fixations in 15 cognitively able males with autism and 15 age-, sex-, and verbal IQ-matched control subjects. We reliably coded fixations on 4 regions: mouth, eyes, body, and objects. Statistical analyses compared fixation time on regions of interest between groups and

correlation of fixation time with outcome measures of social competence (ie, standardized measures of daily social adjustment and degree of autistic social symptoms). **RESULTS:** Significant between-group differences were obtained for all 4 regions. The best predictor of autism was reduced eye region fixation time. Fixation on mouths and objects was significantly correlated with social functioning: increased focus on mouths predicted improved social adjustment and less autistic social impairment, whereas more time on objects predicted the opposite relationship. **CONCLUSIONS:** When viewing naturalistic social situations, individuals with autism demonstrate abnormal patterns of social visual pursuit consistent with reduced salience of eyes and increased salience of mouths, bodies, and objects. Fixation times on mouths and objects but not on eyes are strong predictors of degree of social competence.

3.1.28. Hillier, A., Allinson, L. "Beyond expectations: autism, understanding embarrassment, and the relationship with theory of mind." *Autism* 2002 Sep;6(3):299-314.

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The ability of high-functioning individuals with autism to understand the complex emotion of embarrassment, and how this relates to an understanding of theory of mind, was investigated. Scenarios involving embarrassing and non-embarrassing situations were presented to a group with autism and three comparison groups. Participants were required to rate the level of embarrassment felt by the protagonist and to justify their choices. The results indicated that those with autism generally gave similar ratings of embarrassment as the comparison groups, but did show significant difficulty with non-embarrassing scenarios, and in providing appropriate justifications for embarrassment. In addition, a significant relationship between scores from false belief tasks and justification scores was found, supporting the proposed link between theory of mind skills and understanding embarrassment. Participants with autism did, however, show a higher than expected understanding of this complex emotion.

3.1.29. Rinehart, N.J., Bradshaw, J.L., Brereton, A.V., Tonge, B.J. "Lateralization in individuals with high-functioning autism and Asperger's disorder: a frontostriatal model." *J Autism Dev Disord* 2002 Aug;32(4):321-331.

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Neurobiological and behavioural studies of possible left hemisphere dysfunction in autism have generated conflicting results. Left hemisphere dysfunction may manifest in autism only in tasks that invoke executive functions. Moreover, left hemisphere dysfunction may underpin autism but not Asperger's disorder. We thus aimed to systematically investigate reports of anomalous lateralization in individuals with high-functioning autism and Asperger's disorder. Two of the tasks were sensitive to executive dysfunction: a serial choice reaction-time task and a Posner-type paradigm; the

remaining tasks instead investigated aspects of perceptual lateralisation. Compared with age- and IQ-matched controls, the autism group displayed deficiencies in right hemisphere (and by implication, left hemisphere) performance on both executive function tasks; however, this group demonstrated normal lateralization effects on the nonexecutive, visual-perceptual tasks. In contrast, the Asperger's disorder group showed similar laterality effects to their age- and IQ-matched controls on both executive and nonexecutive function tasks. The etiological relevance of this neurobehavioral dissociation between high-functioning autism and Asperger's disorder was discussed; in particular, it was suggested that the period where dominance shifts from right to left hemisphere is important in whatever process might dictate the emergence of either autism or Asperger's disorder.

3.1.30. Ghaziuddin, M., Ghaziuddin, N., Greden, J. "Depression in persons with autism: implications for research and clinical care." *J Autism Dev Disord* 2002 Aug;32(4):299-306. Publication Types: Review, Review, Academic.

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Although several studies have investigated the occurrence of medical and neurological conditions in persons with autism, relatively few reports have focused on the phenomenology and treatment of psychiatric disorders in this population. There is emerging evidence that depression is probably the most common psychiatric disorder that occurs in autistic persons. In this review, we examine the factors that influence the presence of depression in this population, such as the level of intelligence, age, gender, associated medical conditions, and the role of genetic factors and life events. We discuss the various forms of treatment available and highlight the need for early detection.

3.1.31. Pelphrey, K.A., Sasson, N.J., Reznick, J.S., Paul, G., Goldman, B.D., Piven, J. "Visual scanning of faces in autism." *J Autism Dev Disord* 2002 Aug;32(4):249-61.

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The visual scanpaths of five high-functioning adult autistic males and five adult male controls were recorded using an infrared corneal reflection technique as they viewed photographs of human faces. Analyses of the scanpath data revealed marked differences in the scanpaths of the two groups. The autistic participants viewed nonfeature areas of the faces significantly more often and core feature areas of the faces (i.e., eyes, nose, and mouth) significantly less often than did control participants. Across both groups of participants, scanpaths generally did not differ as a function of the instructions given to the participants (i.e., "Please look at the faces in any manner you wish." vs. "Please identify the emotions portrayed in these faces."). Autistic participants showed a deficit in emotion recognition, but this effect was driven primarily by deficits in the recognition of fear.

Collectively, these results indicate disorganized processing of face stimuli in autistic individuals and suggest a mechanism that may subserve the social information processing deficits that characterize autism spectrum disorders.

3.1.32. Huang, H.L., Shieh, Y.L., Wu, H.J., Chuang, S.F., Yang, P., Jong, Y.J. "Asperger's syndrome and aberrant neurofunctional organization—a case report." *Kaohsiung J Med Sci* 2002 Apr;18(4):198-204.

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Asperger's Syndrome (AS) is a severe developmental disorder characterized primarily by marked and sustained difficulties in social interaction and unusual patterns of circumscribed interests and behavioral peculiarities. AS differs from autism primarily in that there is no general delay or retardation in language. A 3.5 year-old boy with AS was referred for psychological assessment and treatment. When the boy was 23 months old, he was assessed with Bayley Scales of Infant Development (2nd ed.). Both MDI and PDI were within normal limits. After the referral, this boy was assessed with WPPSI-R and then prescribed 5 weekly intervention sessions consisting of communication skills training. At a one week's follow-up the boy was reassessed with Leiter-R. The results of WPPSI-R and Leiter-R showed the boy was in the normal intelligence range. From the second session to the fifth session, the boy's mother recorded 526 of his utterances. According to the analysis of these speech data, the language development for this boy was at Stage V, which indicated that his language development was in the superior range for his age. After 5 intervention sessions, the improvements in the child's communication skills were such that no further sessions were warranted. This boy might represent a case of aberrant neurofunctional organization. He has defects in perceptual organization but has good pattern recognition, which is based on features. It is theorized that his excellent verbal ability competed with the perceptual organization, so that he compensated for perceptual organization with verbal ability. An intervention designed to inhibit verbal compensation and facilitate configural processing is recommended.

3.1.33. Minshew, N.J., Meyer, J., Goldstein, G. "Abstract reasoning in autism: a dissociation between concept formation and concept identification." *Neuropsychology* 2002 Jul;16(3):327-34.

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The concept identification and concept formation aspects of abstract reasoning were examined in 90 nonmentally retarded individuals with autism and 107 normal controls. It was hypothesized that pronounced deficits would be found on concept formation tests, whereas performance on concept identification tests would be relatively intact. There was a significant difference between individuals with autism and individuals from a matched control group on all abstract reasoning tasks, but, with the exception of the Wisconsin Card Sorting Test (R. K. Heaton et al., 1993), differences on concept

identification tests were not clinically significant. Factor analyses showed that concept formation and concept identification tasks loaded on separate factors in the autism group but not in the control group. Stepwise discriminant function analyses revealed that 2 tests of concept formation correctly classified 78.4% of cases, whereas concept identification tasks did not pass the tolerance test.

3.1.34. Castelli, F., Frith, C., Happe, F., Frith, U. "Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes." *Brain* 2002 Aug;125(Pt 8):1839-49.

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Ten able adults with autism or Asperger syndrome and 10 normal volunteers were PET scanned while watching animated sequences. The animations depicted two triangles moving about on a screen in three different conditions: moving randomly, moving in a goal-directed fashion (chasing, fighting), and moving interactively with implied intentions (coaxing, tricking). The last condition frequently elicited descriptions in terms of mental states that viewers attributed to the triangles (mentalizing). The autism group gave fewer and less accurate descriptions of these latter animations, but equally accurate descriptions of the other animations compared with controls. While viewing animations that elicited mentalizing, in contrast to randomly moving shapes, the normal group showed increased activation in a previously identified mentalizing network (medial prefrontal cortex, superior temporal sulcus at the temporo-parietal junction and temporal poles). The autism group showed less activation than the normal group in all these regions. However, one additional region, extrastriate cortex, which was highly active when watching animations that elicited mentalizing, showed the same amount of increased activation in both groups. In the autism group this extrastriate region showed reduced functional connectivity with the superior temporal sulcus at the temporo-parietal junction, an area associated with the processing of biological motion as well as with mentalizing. This finding suggests a physiological cause for the mentalizing dysfunction in autism: a bottleneck in the interaction between higher order and lower order perceptual processes.

3.1.35. Trepagnier, C., Sebrechts, M.M., Peterson, R. "Atypical face gaze in autism." *Cyberpsychol Behav* 2002 Jun;5(3):213-7.

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An eye-tracking study of face and object recognition was conducted to clarify the character of face gaze in autistic spectrum disorders. Experimental participants were a group of individuals diagnosed with Asperger's disorder or high-functioning autistic disorder according to their medical records and confirmed by the Autism Diagnostic Interview-Revised (ADI-R). Controls were selected on the basis of age, gender, and educational level to be comparable to the experimental group. In order to maintain attentional focus,

stereoscopic images were presented in a virtual reality (VR) headset in which the eye-tracking system was installed. Preliminary analyses show impairment in face recognition, in contrast with equivalent and even superior performance in object recognition among participants with autism-related diagnoses, relative to controls. Experimental participants displayed less fixation on the central face than did control-group participants. The findings, within the limitations of the small number of subjects and technical difficulties encountered in utilizing the helmet-mounted display, suggest an impairment in face processing on the part of the individuals in the experimental group. This is consistent with the hypothesis of disruption in the first months of life, a period that may be critical to typical social and cognitive development, and has important implications for selection of appropriate targets of intervention.

3.1.36. van der Geest, J.N., Kemner, C., Verbaten, M.N., van Engeland, H. "Gaze behavior of children with pervasive developmental disorder toward human faces: a fixation time study." *J Child Psychol Psychiatry* 2002 Jul;43(5):669-78.

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BACKGROUND: The abnormal gaze behavior of autistic children toward human faces, as observed in daily-life situations, are investigated in two fixation time studies. It has been argued that faces are a special kind of stimuli for normal individuals and that this might not be the case for autistic children. **METHODS:** A group of high-functioning autistic children (including a group of sub-threshold PDD-NOS children) was compared with a group of normal children, with respect to their fixation behavior for photographs of human faces. Using an infrared eye-tracking device, fixation times for the whole face and for the facial elements of faces were compared between the two groups. The first study dealt with faces having an emotional expression. The second study dealt with neutral faces presented either upright or upside-down. **RESULTS:** Results of the two studies showed that autistic children have the same fixation behavior as normal children for upright faces, with or without an emotional expression. Furthermore, results of the second study showed that normal children spent less time looking at upside-down faces, but that the fixation times of autistic children were not influenced by the orientation of the faces. **CONCLUSIONS:** These results plead against the notion that the abnormal gaze behavior in everyday life is due to the presence of facial stimuli per se. Furthermore, the absence of a face orientation effect in autistic children might be a reflection of a lack of holistic processing of human faces in autism.

3.1.37. Green, D., Baird, G., Barnett, A.L., Henderson, L., Huber, J., Henderson, S.E. "The severity and nature of motor impairment in Asperger's syndrome: a comparison with specific developmental disorder of motor function." *J Child Psychol Psychiatry* 2002 Jul;43(5):655-68.

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BACKGROUND: The aims of this study were to measure objectively the extent and severity of motor impairment in children with Asperger's syndrome and to determine whether the motor difficulties experienced by such children differed in any way from those classified as having a Specific Developmental Disorder of Motor Function (SDD-MF). Criteria derived from ICD 10-R were used to identify 11 children with Asperger's syndrome and a matched group of 9 children with a Specific Developmental Disorder of Motor Function. Children in both groups were required to have a verbal IQ of 80 or greater on the WISC III-R. **METHOD:** The Autism Diagnostic Interview (Revised; Lord, Rutter, & LeCouteur, 1994) was used to identify features of AS in the first group and to exclude them in the latter. The Movement Assessment Battery for Children (Henderson & Sugden, 1992) provided a standardised test of motor impairment. A Gesture Test based on that by Cermak, Coster, and Drake (1980) was used to assess the child's ability to mime the use of familiar tools and to imitate meaningless sequences of movements. **RESULTS:** All the children with Asperger's syndrome turned out to meet our criterion for a diagnosis of motor impairment, five of the six most severely motor impaired children in the whole study being from this group. Performance of the Asperger group was also slightly poorer on the Gesture Test. The profile of performance on each test was examined in detail but no evidence of group differences in the pattern of impairment was found. **CONCLUSIONS:** This study is consistent with others suggesting a high prevalence of clumsiness in Asperger's syndrome. Our findings also attest to the widespread prevalence of motor impairment in developmental disorders and the problems such co-morbidity poses for attempts to posit discrete and functionally coherent impairments underlying distinct syndromes.

3.1.38. Ropar, D., Mitchell, P. "Shape constancy in autism: the role of prior knowledge and perspective cues." *J Child Psychol Psychiatry* 2002 Jul;43(5):647-53.

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BACKGROUND: Evidence suggests that individuals with autism may not attend to contextual information (conceptual or perceptual) when processing stimuli (Frith 1989; Shah & Frith, 1983). **METHOD:** We investigated the role of prior knowledge and perspective cues when judging the shape of a slanted circle in individuals with and without autism. Individuals adjusted a shape on a computer screen to appear the same as a slanted circle. **RESULTS:** Participants in all groups (autistic, moderate learning difficulties, children aged 9 years and adults) exaggerated circularity. Strikingly, however, individuals with autism were unique in exaggerating circularity significantly far less when perspective cues surrounding the slanted circle were eliminated. Prior knowledge that the shape was a slanted circle provoked a strong exaggeration effect in participants without autism, but not in those with autism. **CONCLUSIONS:** Perhaps classifying the stimulus as a 'circle' was sufficient to provoke a strong exaggeration effect in those without (but not with) autism. In this domain, we show that perception in autism

may be less influenced by prior knowledge, and therefore less 'top-down'.

3.1.39. Shamay-Tsoory, S.G., Tomer, R., Yaniv, S., Aharon-Peretz, J. "Empathy deficits in Asperger syndrome: a cognitive profile." *Neurocase* 2002;8(3):245-52. Publication Types: Clinical Trial.

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Although lack of empathy has been considered a central characteristic of Asperger syndrome, quantitative and qualitative assessments of empathy in this syndrome are lacking. We present two cases of adolescents with Asperger syndrome who show extreme deficits on measures of both cognitive and affective empathy. Analysis of their performance on tasks assessing cognitive and affective processing did not reveal significant impairment in executive functions, nor in their ability to recognize emotions or the ability to create a mental representation of another person's knowledge. However, both patients were unable to integrate the emotional content with mental representations and deduce the other person's emotional state. These results suggest that impaired empathy in individuals with Asperger syndrome may be due to impaired integration of the cognitive and affective facets of the other person's mental state.

3.1.40. Lincoln, A., Lai, Z., Jones, W. "Shifting attention and joint attention dissociation in Williams syndrome: implications for the cerebellum and social deficits in autism." *Neurocase* 2002;8(3):226-32. Publication Types: Clinical Trial.

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An experimental paradigm that assesses one's capacity to perform intermodality attention shifting has proved to be sensitive for persons with cerebellar dysfunction. The basic experiment includes three conditions, auditory focus, visual focus and shift attention. In the auditory focus condition, the participant is instructed to press a joystick button when they hear the target tone and to ignore the other tone and the two visual stimuli. In the visual focus condition, the participant is instructed to press only the button to the target colored square and to ignore the other colored square and the two tones. In the shift attention condition, the participant is instructed to press the button to the first auditory target and then to press to the next visual target. They are instructed to continue to alternate their responses between auditory and visual targets until the trial is complete. Three individuals with Williams Syndrome (WMS), a genetic disorder due to the deletion of the elastin gene, were examined under these experimental conditions. Each participant with WMS had previously completed magnetic resonance imaging, and mid-sagittal area measurements had been made of the vermal lobules I-V and VI-VII. Cases were selected on the basis of cerebellar findings: one case was hypoplastic, one was hyperplastic and one had measurements in a range within one standard deviation of

average for normal controls. Each of the WMS participants showed a pattern of being impaired in being able to shift their attention rapidly when cue-to-target intervals were less than 2.5 s. Their performance was very similar to previous reports of persons with cerebellar abnormalities and persons with autism. All three participants improved their target accuracy when given more time to shift their attention. The three participants did not experience performance deficits to either long or short cue-to-target intervals in the auditory focus or visual focus conditions. The results are consistent with the presence of cerebellar dysfunction, and are the first to suggest problems with shifting attention in persons with WMS. However, the three WMS participants demonstrated normal joint attention and had none of the social deficits observed in persons with autism.

3.1.41. Bolte, S., Rudolf, L., Poustka, F. **"The cognitive structure of higher functioning autism and schizophrenia: a comparative study."** *Compr Psychiatry* 2002 Jul-Aug;43(4):325-30.

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The purpose of this study was to examine whether performance on a standard cognitive test-battery can be used to clearly separate higher functioning autism from schizophrenia. Revised Wechsler Intelligence Scale for Children (WISC-R) or Adults (WAIS-R) profiles of 20 autistic and 20 schizophrenic adolescent young adult subjects matched for age, sex, and IQ level were contrasted. On average, autistic individuals had higher values on the subtest "Similarities," while schizophrenic participants scored better on "Comprehension." Discriminant analysis showed that a prognosis of the psychiatric classification can be made with 82.5% accuracy if all subscale data are considered. Even though this finding probably has limited merit for making judgements in clinical practice, it might be of exploratory value in the pursuit of differentiating autism and schizophrenia on a cognitive level. Copyright 2002, Elsevier Science (USA). All rights reserved.

3.1.42. McAlonan, G.M., Daly, E., Kumari, V., Critchley, H.D., van Amelsvoort, T., Suckling, J., Simmons, A., Sigmundsson, T., Greenwood, K., Russell, A., Schmitz, N., Happe, F., Howlin, P., Murphy, D.G. **"Brain anatomy and sensorimotor gating in Asperger's syndrome."** *Brain* 2002 Jul;125(Pt 7):1594-606. Publication Types: Clinical Trial, Controlled Clinical Trial.

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Asperger's syndrome (an autistic disorder) is characterized by stereotyped and obsessional behaviours, and pervasive abnormalities in socio-emotional and communicative behaviour. These symptoms lead to social exclusion and a significant healthcare burden; however, their neurobiological basis is poorly understood. There are few studies on brain anatomy of Asperger's syndrome, and no focal anatomical abnormality has been reliably reported from brain imaging

studies of autism, although there is increasing evidence for differences in limbic circuits. These brain regions are important in sensorimotor gating, and impaired 'gating' may partly explain the failure of people with autistic disorders to inhibit repetitive thoughts and actions. Thus, we compared brain anatomy and sensorimotor gating in healthy people with Asperger's syndrome and controls. We included 21 adults with Asperger's syndrome and 24 controls. All had normal IQ and were aged 18-49 years. We studied brain anatomy using quantitative MRI, and sensorimotor gating using prepulse inhibition of startle in a subset of 12 individuals with Asperger's syndrome and 14 controls. We found significant age-related differences in volume of cerebral hemispheres and caudate nuclei (controls, but not people with Asperger's syndrome, had age-related reductions in volume). Also, people with Asperger's syndrome had significantly less grey matter in fronto-striatal and cerebellar regions than controls, and widespread differences in white matter. Moreover, sensorimotor gating was significantly impaired in Asperger's syndrome. People with Asperger's syndrome most likely have generalized alterations in brain development, but this is associated with significant differences from controls in the anatomy and function of specific brain regions implicated in behaviours characterizing the disorder. We hypothesize that Asperger's syndrome is associated with abnormalities in fronto-striatal pathways resulting in defective sensorimotor gating, and consequently characteristic difficulties inhibiting repetitive thoughts, speech and actions.

3.1.43. Carpenter, M., Pennington, B.F., Rogers, S.J. **"Interrelations among social-cognitive skills in young children with autism."** *J Autism Dev Disord* 2002 Apr;32(2):91-106.

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Typically developing infants show a reliable developmental sequence of emergence of early social-cognitive skills, such as joint attention, communicative gestures, gaze and point following, imitation, and referential language. First infants share others' attention, then they follow others' attention and then behavior, and then they direct others' attention and then behavior. The current study used a series of tests from a study of typically developing infants (Carpenter, Nagell, & Tomasello, 1998) to investigate interrelations among these social-cognitive skills in young children with autism and children with other developmental delays. Tests of object permanence, spatial relations, facial and manual imitation, and executive function also were included. We found that for most children with autism, unlike other children, tests involving others' attention were more difficult than tests involving others' behavior. However, within the domains of attention and behavior, the typical pattern of sharing, then following, and then directing was evident. There were several positive intercorrelations among the social-cognitive skills (as there were for typically developing infants), but there also was some evidence of individual differences in patterns. Implications for theories of social-cognitive and language development are discussed.

3.1.44. van der Geest, J.N., Kemner, C., Camfferman, G., Verbaten, M.N., van Engeland, H. "Looking at images with human figures: comparison between autistic and normal children." *J Autism Dev Disord* 2002 Apr;32(2):69-75.

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Based on clinical observations of abnormal gaze behavior of autistic children, it has been suggested that autistic children have a problem in processing social information. Several studies on eye movements have indeed found indications that children with autism show particularly abnormal gaze behavior in relation to social stimuli. However, the methodology used in such investigations did not allow for precise gaze analysis. In the present study, the looking behavior of autistic children toward cartoon-like scenes that included a human figure was measured quantitatively using an infrared eye-tracking device. Fixation behavior of autistic children was similar to that of their age- and IQ-matched normal peers. These results do not support the notion that autistic children have a specific problem in processing socially loaded visual stimuli. Also, there is no indication for an abnormality in gaze behavior in relation to neutral objects. It is suggested that the often-reported abnormal use of gaze in everyday life is not related to the nature of the visual stimuli but that other factors, like social interaction, may play a decisive role.

3.1.45. Deuel, R.K. "Autism: a cognitive developmental riddle." *Pediatr Neurol* 2002 May;26(5):349-57. Publication Types: Review, Review, Tutorial.

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It has been 60 years since the definitive descriptions of autism, yet it is only in the past decade that related advances in cognitive and basic neuroscience have begun to be incorporated in clinical practice. Some of the resultant clinical advances, which include a trend toward international standardization of diagnosis on the basis of behavioral criteria and which, in turn, seem to allow for earlier, more secure diagnosis and the application of behavioral therapy in early childhood, as well as more thorough genetic studies, are briefly reviewed. The three major defects in thought processing that are postulated by cognitive neuropsychologists to result in aberrant autistic behaviors are also reviewed and linked to recent functional imaging studies in autistic patients and some animal and bench research suggestive of both cortical and subcortical developmental vulnerabilities in autism. Overall it seems at least possible that neuroscientific research may yield results applicable to prevention or remediation of autism, a condition heretofore considered irremediable.

3.1.46. Siegal, M., Varley, R. "Neural systems involved in 'theory of mind'". *Nat Rev Neurosci* 2002 Jun;3(6):463-71. Publication Types: Review, Review, Academic.

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What is the nature of our ability to understand and reason about the beliefs of others—the possession of a "theory of mind", or ToM? Here, we review findings from imaging and lesion studies indicating that ToM reasoning is supported by a widely distributed neural system. Some functional components of this system, such as language-related regions of the left hemisphere, the frontal lobes and the right temporal parietal cortex, are not solely dedicated to the computation of mental states. However, the system also includes a core, domain-specific component that is centred on the amygdala circuitry. We provide a framework in which impairments of ToM can be viewed in terms of abnormalities of the core system, the failure of a co-opted system that is necessary for performance on a particular set of tasks, or the absence of an experiential trigger for the emergence of ToM.

3.1.47. Dawson, G., Carver, L., Meltzoff, A.N., Panagiotides, H., McPartland, J., Webb, S.J. "Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development." *Child Dev* 2002 May-Jun;73(3):700-17.

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This study utilized electroencephalographic recordings to examine whether young children with autism spectrum disorder (ASD) have impaired face recognition ability. High-density brain event-related potentials (ERPs) were recorded to photos of the child's mother's face versus an unfamiliar female face and photos of a favorite versus an unfamiliar toy from children with ASD, children with typical development, and children with developmental delay, all 3 to 4 years of age (N = 118). Typically developing children showed ERP amplitude differences in two components, P400 and Nc, to a familiar versus an unfamiliar face, and to a familiar versus an unfamiliar object. In contrast, children with ASD failed to show differences in ERPs to a familiar versus an unfamiliar face, but they did show P400 and Nc amplitude differences to a familiar versus an unfamiliar object. Developmentally delayed children showed significant ERP amplitude differences for the positive slow wave for both faces and objects. These data suggest that autism is associated with face recognition impairment that is manifest early in life.

3.1.48 Brock, J., Brown, C.C., Boucher, J., Rippon, G. "The temporal binding deficit hypothesis of autism." *Dev Psychopathol* 2002 Spring;14(2):209-24. Publication Types: Review, Review Literature.

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Frith has argued that people with autism show "weak central coherence," an unusual bias toward piecemeal rather than configurational processing and a reduction in the normal tendency to process information in context. However, the precise cognitive and neurological mechanisms underlying weak central coherence are still unknown. We propose the hypothesis that the features of autism associated with weak central coherence result from a reduction in the integration of

specialized local neural networks in the brain caused by a deficit in temporal binding. The visuo-perceptual anomalies associated with weak central coherence may be attributed to a reduction in synchronization of high-frequency gamma activity between local networks processing local features. The failure to utilize context in language processing in autism can be explained in similar terms. Temporal binding deficits could also contribute to executive dysfunction in autism and to some of the deficits in socialization and communication.

3.1.49. Megarbane, A., Hersh, J.H., Chouery, E., Fabre, M. **"Craniosynostosis, telecanthus, scalp hair abnormalities, and sensorineural deafness in two sibs."** *Am J Med Genet* 2002 May 15;109(4):323-7.

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A sister and a brother with anomalous skull configuration, facial abnormalities, abnormal scalp hair growth, sensorineural hearing loss and, in the boy, proven craniosynostosis, severe mental retardation, and autism were reported in 1986 in an abstract by Hersh et al. We reexamined this family and here review the literature focusing on the major clinical findings, and suggest that their clinical manifestations may represent a previously unreported syndrome. Copyright 2002 Wiley-Liss, Inc.

3.1.50. Dawson, G., Munson, J., Estes, A., Osterling, J., McPartland, J., Toth, K., Carver, L., Abbott, R. **"Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay."** *Child Dev* 2002 Mar-Apr;73(2):345-58.

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Studies have shown that young children with autism are not impaired on prefrontal tasks relative to what would be expected for their mental age, raising questions about the executive dysfunction hypothesis of autism. These studies did not include ventromedial prefrontal tasks, however. The present study examined whether young children with autism spectrum disorder (ASD) are impaired on ventromedial prefrontal tasks, and whether performance on such tasks is correlated with a core autism symptom, joint attention ability. Seventy-two 3- to 4-year-old children with ASD, 34 3- to 4-year-old developmentally delayed children, and 39 12- to 46-month-old typically developing children, matched on mental age, were administered ventromedial and dorsolateral prefrontal tasks and joint attention tasks. Children with ASD performed similarly to comparison groups on all executive function tasks, indicating that at this early age, there is no autism-specific pattern of executive dysfunction. Ventromedial, but not dorsolateral, prefrontal task performance was strongly correlated with joint attention ability, however. The ventromedial prefrontal cortex is hypothesized to play a role in the development of joint attention and possibly some aspects of the autistic syndrome.

3.1.51. Calder, A.J., Lawrence, A.D., Keane, J., Scott, S.K., Owen, A.M., Christoffels, I., Young, A.W. **"Reading the mind from eye gaze."** *Neuropsychologia* 2002;40(8):1129-38.

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Baron-Cohen [Mindblindness: an essay on autism and theory of mind. Cambridge, MA: MIT Press, 1997] has suggested that the interpretation of gaze plays an important role in a normal functioning theory of mind (ToM) system. Consistent with this suggestion, functional imaging research has shown that both ToM tasks and eye gaze processing engage a similar region of the posterior superior temporal sulcus (STS). However, a second brain region associated with ToM, the medial prefrontal (MPF) cortex, has not been identified by previous eye gaze studies. We discuss the methodological issues that may account for the absence of MPF activation in these experiments and present a PET study that controls for these factors. Our experiment included three conditions in which the proportions of faces gazing at, and away from, the participant, were as follows: 100% direct [0% averted], 50% direct-50% averted, and 100% horizontally averted [0% direct]. Two control conditions were also included in which the faces' gaze were averted down, or their eyes were closed. Contrasts comparing the gaze conditions with each of the control conditions revealed medial frontal involvement. Parametric analyses showed a significant linear relationship between increasing proportions of horizontally averted gaze and increased rCBF in the MPF cortex. The opposite parametric analysis (increasing proportions of direct gaze) was associated with increased rCBF in a number of areas including the superior and medial temporal gyri. Additional subtraction contrasts largely confirmed these patterns. Our results demonstrate a considerable degree of overlap between the medial frontal areas involved in eye gaze processing and theory of mind tasks.

3.1.52. Kemner, C., Oranje, B., Verbaten, M.N., van Engeland, H. **"Normal P50 gating in children with autism."** *J Clin Psychiatry* 2002 Mar;63(3):214-7.

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BACKGROUND: An important characteristic of children with autism is their unusual reaction to stimuli, which may be related to problems in the filtering of sensory input. For this reason, sensory filtering was measured in children with autism using the P50 gating paradigm. **METHOD:** Twelve non-mentally retarded children with autism (i.e., having a DSM-IV diagnosis of either autistic disorder or pervasive developmental disorder not otherwise specified) and 11 healthy control children were tested for their ability to suppress P50, measured at the Cz electrode. **RESULTS:** No differences were found between the children with autism and the control children with regard to absolute P50 amplitudes and P50 suppression. **CONCLUSION:** The excitability of the neuronal substrate that causes P50 is normal in children with autism, as are the early, inhibitory processes related to P50

gating. These results distinguish between subjects with autism and subjects with schizophrenia, in whom sensory gating is abnormal.

3.1.53. Estecio, M., Fett-Conte, A.C., Varella-Garcia, M., Fridman, C., Silva, A.E. "Molecular and cytogenetic analyses on Brazilian youths with pervasive developmental disorders." *J Autism Dev Disord* 2002 Feb;32(1):35-41.

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The Pervasive Developmental Disorders (PDDs) constitute a group of behavioral and neurobiological impairment conditions whose main features are delayed communicative and cognitive development. Genetic factors are reportedly associated with PDDs and particular genetic abnormalities are frequently found in specific diagnostic subgroups such as the autism spectrum disorders. This study evaluated cytogenetic and molecular parameters in 30 youths with autism or other PDDs. The fragile X syndrome was the most common genetic abnormality detected, presented by 1 patient with autism and 1 patient with PPD not-otherwise specified (PPD-NOS). One girl with PDD-NOS was found to have tetrasomy for the 15q11-q13 region, and one patient with autism exhibited in 2/100 metaphases an inv(7)(p35q36), thus suggesting a mosaicism 46,XX/46,XX,inv(7)(p15q36) or representing a coincidental finding. The high frequency of chromosomopathies support the hypothesis that PDDs may develop as a consequence to chromosomal abnormalities and justify the cytogenetic and molecular assessment in all patients with PDDs for establishment of diagnosis.

3.1.54. Toichi, M., Kamio, Y. "Long-term memory and levels-of-processing in autism." *Neuropsychologia* 2002;40(7):964-9.

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Prior studies reported that long-term memory (LTM) was basically unimpaired in individuals with autism. However, people with autism have been found to perform worse than ability-matched controls when verbal materials to be remembered are semantically related. In normal subjects, semantic processing of verbal materials facilitates LTM better than 'shallow' (phonological or perceptual) processing, which is known as the levels-of-processing effect. In this study, the relationship between LTM and semantic processing was investigated using a levels-of-processing task. In Study 1, a levels-of-processing task was conducted on healthy volunteers, which confirmed the levels-of-processing effect with our task. In study 2, the same task was conducted on autistic subjects with mild or no mental retardation and ability-matched controls. The levels-of-processing effect was confirmed in the control group. Although overall performance in the two groups was comparable, the levels-of-processing effect was not found in the autistic group. LTM resulting from perceptual processing was better in the autistic group than in the control group, indicating superior "rote memory" in

individuals with autism. Furthermore, the pattern of correlations between LTM performance and cognitive measures differed greatly between the two groups. The lack of the levels-of-processing effect, which has not been reported in other psychiatric or neuropathological conditions, suggests an abnormal relationship between semantic memory and episodic memory in individuals with autism.

3.1.55. Grelotti, D.J., Gauthier, I., Schultz, R.T. "Social interest and the development of cortical face specialization: what autism teaches us about face processing." *Dev Psychobiol* 2002 Apr;40(3):213-25. Publication Types: Review, Review, Academic.

Child Study Center and Developmental Neuroimaging Program, Yale University, School of Medicine, New Haven, CT 06520-7900, USA.

Investigations of face processing in persons with an autism spectrum disorder (ASD) inform upon theories of the development of "normal" face processing, and the story that emerges challenges some models of the nature and origin of cortical face specialization. Individuals with an ASD possess deficits in face processing and a lack of a fusiform face area (FFA). Evidence from studies of ASD can be conceptualized best using an expertise framework of face processing rather than models that postulate a face module in the fusiform gyrus. Because persons with an ASD have reduced social interest, they may fail to develop cortical face specialization. Face specialization may develop in normal individuals because they are socially motivated to regard the face, and such motivation promotes expertise for faces. The amygdala is likely the key node in the system that marks objects as emotionally salient and could be crucial to the development of cortical face specialization. Copyright 2002 Wiley Periodicals, Inc.

3.1.56. Kaya, M., Karasalioglu, S., Ustun, F., Gultekin, A., Cermik, T.F., Fazlioglu, Y., Ture, M., Yigitbasi, O.N., Berkarda, S. "The relationship between 99mTc-HMPAO brain SPECT and the scores of real life rating scale in autistic children." *Brain Dev* 2002 Mar;24(2):77-81.

Department of Nuclear Medicine, Faculty of Medicine, Trakya University, Tip Fakultesi, Nukleer Tip ABD 22030, Edirne, Turkey. meryemk@trakya.edu.tr

Childhood autism is a developmental disability of unknown origin with probable multiple etiologies. The purpose of this study was to compare the changes of regional cerebral blood flow (rCBF) in autistic and non-autistic controls, and to determine the relationship between rCBF on 99mTc-hexamethylpropylene amine oxime (HMPAO) brain SPECT and the scores of the Ritvo-Freeman Real Life Rating Scale (RLRS), IQ levels, and age of autistic children. Eighteen autistic children (four girls, 14 boys; mean age: 6.13 +/- 1.99 years) and 11 non-autistic controls (five girls, six boys, mean age: 6.5 +/- 3.39 years) were examined using 99mTc-HMPAO brain SPECT. All the children satisfying DSM-IV criteria for autistic disorder were taken into evaluation, and scored by the Ritvo-Freeman RLRS. IQ levels of these children were

determined by Goodenough IQ test. Six cortical regions of interest (ROIs; frontal (F), parietal (P), frontotemporal (FT), temporal (T), temporo-occipital (TO), and occipital (O)) were obtained on transaxial slices for count data acquisition. The ratio of average counts in each ROI to whole-slice counts for the autistic children was correlated with the scores of Ritvo-Freeman RLRS. Hypoperfusion in rCBF in autistic children compared with the control group were identified in bilateral F, FT, T, and TO regions. We found no relationship between rCBF on ^{99m}Tc-HMPAO brain SPECT and the scores of the Ritvo-Freeman RLRS. There was a relationship between bilateral F regions perfusion on ^{99m}Tc-HMPAO brain SPECT and the age of autistic children. There was also a negative correlation between IQ levels and the scores of sensory responses, social relationship to people, and sensory-motor responses. Our results suggest that ^{99m}Tc-HMPAO brain SPECT is helpful to locate the perfusion abnormalities but no correlation is found between rCBF on ^{99m}Tc-HMPAO brain SPECT and the scores of Ritvo-Freeman RLRS.

3.1.57. Hellings, J.A., Hossain, S., Martin, J.K., Baratang, R.R. "Psychopathology, GABA, and the Rubinstein-Taybi syndrome: a review and case study." *Am J Med Genet* 2002 Mar 8;114(2):190-5. Publication Types: Review, Review of Reported Cases.

University of Kansas Medical Center, Department of Psychiatry, Kansas City, Kansas, USA.

An adult female with congenital Rubinstein-Taybi syndrome (RTS) and severe mental retardation is described, who presented with symptoms of severe over-activity, short attention span, mood lability, and aggressive outbursts in a cyclical pattern, suggestive of recurrent manic-like episodes. These symptoms improved significantly with divalproex (Depakote) monotherapy. Review of the existing studies showed that 10-76% of persons with RTS may be identified with similar behavioral symptoms. We postulate other persons with RTS may respond to divalproex, and there may be some relationship between the chromosome 16p13.3 deletion and gamma-aminobutyric acid (GABA) receptor or neurotransmitter abnormalities. Recent molecular genetic studies suggest a linkage of this region to bipolar mood disorder and autism, both of which were diagnosed in this patient. Further prospective study is needed of RTS persons regarding behavioral problems, comorbid psychiatric diagnoses, and treatment responses, correlated with genetic abnormalities. Copyright 2002 Wiley-Liss, Inc.

3.1.58. Morton, R., Sharma, V., Nicholson, J., Broderick, M., Poyser, J. "Disability in children from different ethnic populations." *Child Care Health Dev* 2002 Jan;28(1):87-93.

Ronnie Mackeith Child Development Centre, Derbyshire Childrens' Hospital, Derby, UK.

We report on the prevalence of severe neurodisability in children in the Southern Derbyshire Health Authority from different ethnic groups. Information was obtained from the health records of children at the Child Development Centre (CDC), and analysed according to ethnic group. There were

53 in the Pakistani group, 20 in the Indian group and 764 in a mixed group, of which 95% were of European origin. It was estimated that all children with severe disability in the area of the Health Authority had notes at the CDC, except for 10% of the mixed group living on the periphery. The numbers of children with different disabling conditions were recorded, together with a measure of the level of individual disability; the 'Disability Scores'. We also noted if the condition was genetic or chromosomal in origin. Pakistani children showed a higher prevalence than the other groups of severe learning disorder, severe and profound hearing loss and severe visual problems. They also had a slightly increased prevalence of autism and cerebral palsy. Conversely, they showed a lower prevalence of language disorder. Disability scores for Pakistani children attending the CDC were higher than for other groups. Genetic disease causing disability was 10 times more common in the Pakistani children than other ethnic groups. Disability is more common in Pakistani children probably as a result of the cultural practice of consanguineous marriages. This community needs special help for disabled children, and their families, for general support and appropriate genetic counselling.

3.1.59. Sweeten, T.L., Posey, D.J., Shekhar, A., McDougale, C.J. "The amygdala and related structures in the pathophysiology of autism." *Pharmacol Biochem Behav* 2002 Mar;71(3):449-55. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Indiana University School of Medicine, 541 Clinical Drive, Room 298, Indianapolis, IN 46202-5111, USA.

Autism is a neurodevelopmental disorder that is defined behaviorally by severe deficiencies in reciprocal social interaction, verbal and nonverbal communication, and restricted interests. The amygdala is involved in the regulation of social behaviors and may be an important site of pathology for the social dysfunction seen in autism. This review focuses on lesion, postmortem, and neuroimaging studies that investigate the amygdala and related structures in this disorder. Other brain regions potentially involved in the neuropathology of autism are also briefly discussed. Although supportive evidence exists for amygdala dysfunction in autism, the currently available data are inconsistent and additional research is needed.

3.1.60. Blair, R.J., Frith, U., Smith, N., Abell, F., Cipolotti, L. "Fractionation of visual memory: agency detection and its impairment in autism." *Neuropsychologia* 2002 ; 40(1): 108-18.

Institute of Cognitive Neuroscience, University College London, Alexandra House, 17 Queen Square, WC1H 3AR, London, UK. J. blair@ucl.ac.uk

It is known that the adult visual memory system is fractionable into functionally independent cognitive subsystems, selectively susceptible to brain damage. In these cognitive subsystems can fractionate developmentally. However, there has been a paucity of systematic investigations. The present study involves the analysis of

visual memory of a population of individuals with autism and age- and VIQ-matched comparison populations. In addition, they were impaired relative to the age-matched comparison group on recognition memory for potential agents (i.e. objects capable of self-propelled motion) whether they were living (cats and horses) or non-living (motorbikes). In contrast, they were selectively superior relative to the VIQ-matched comparison group on recognition memory for such objects as topographical stimuli (buildings) and leaves that clearly do not have agency. The data is interpreted in terms of reduced sensitivity to agency cues in individuals with autism and general information processing capacity.

3.1.61. Gross-Isseroff, R., Hermesh, H., Weizman, A. **"Obsessive compulsive behaviour in autism—towards an autistic-obsessive compulsive syndrome?"** *World J Biol Psychiatry*. 2001 Oct;2(4):193-7.

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A portion of autistic patients exhibit compulsive-like behaviours. In addition it has been suggested that serotonin plays a major role in both obsessive compulsive disorder (OCD) and autistic disorder. Other neurohumors such as endogenous opioids and oxytocin have also been implicated in the two disorders. There is also some pharmacological overlap between the two disorders, as well as some similar neuroimaging studies. These similarities and overlaps have led us to propose a putative OCD-autistic disorder, which should be studied in greater detail.

3.1.62. Cohen, B.I. **"GABA-transaminase, the liver and infantile autism."** *Med Hypotheses* 2001 Dec;57(6):673-4.

ED Laboratories, S. Hackensack, New Jersey 07606, USA. EDS@Pipeline.com

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter of the mammalian brain and the enzyme responsible for catabolism (breakdown in the liver during regulation) is GABA-Transaminase (GABA-T). Recently, Cohen has shown that extremely high GABA levels in the urine and blood were observed for an autistic child. The finding that elevated levels of GABA in the urine and blood are present for an autistic child could explain why autistic features (such as self-stimulatory behavior and language delays, etc.) are found. Increasing the GABA-T enzyme activity for this autistic patient could result in less plasma GABA (after liver regulation) entering into the bloodstream and brain and it is postulated that this could result in a reduction of the autistic features (such as self-stimulatory behavior and language delays, etc.) due to abnormal development of the axon(s) in the corpus callosum.

3.1.63. Bejerot, S., Nylander, L., Lindstrom, E. **"Autistic traits in obsessive-compulsive disorder."** *Nord J Psychiatry* 2001;55(3):169-76.

Department of Neuroscience, Psychiatry, University Hospital, SE-751 85 Uppsala, Sweden.

In contrast to other non-psychotic psychiatric populations, subjects with obsessive-compulsive disorder (OCD) are more prone to have personality disorder from cluster A (the odd and eccentric cluster). The present study aims at further investigating the relationship between these and other personality traits in OCD subjects and their relation to high functioning autism (HFA) and Asperger disorder. Sixty-four subjects with OCD were included. Personality traits were assessed with the Karolinska Scales of Personality (KSP), and personality disorders with DSM-adapted questionnaires. In addition, autistic traits were assessed in 29 videotaped subjects, by 3 independent raters. Twenty percent of the subjects with OCD were identified as also having autistic traits. These subjects scored higher on KSP scales measuring muscular tension, psychasthenia, and inhibition of aggression and lower on socialization as compared with OCD subjects without autistic traits. Additionally, subjects with autistic traits fulfilled criteria for anxious personality disorders and paranoid personality disorders significantly more often than subjects without autistic traits. We propose that OCD is often related to HFA and Asperger disorder. Self-report questionnaires may be useful in establishing the diagnosis. However, those with the most obvious autistic features seem to be less able to identify these traits in themselves.

3.1.64. Teunisse, J.P., de Gelder, B. **"Impaired categorical perception of facial expressions in high-functioning adolescents with autism."** *Neuropsychol Dev Cogn Sect C Child Neuropsychol* 2001 Mar;7(1):1-14.

Department of Psychology, University Medical Centre St. Radboud, Nijmegen, The Netherlands.

Categorical perception of facial expressions is studied in high-functioning adolescents with autism, using three continua of facial expressions obtained by morphing. In contrast to the results of normal adults, the performance on the identification task in autistic subjects did not predict performance on the discrimination task, an indication that autistic individuals do not perceive facial expressions categorically. Performance of autistic subjects with low social intelligence was more impaired than that of subjects with higher social IQ scores on the expression recognition of unmanipulated photographs. It is suggested that autistic subjects with higher social intelligence may use compensatory strategies that they have acquired in social training programs. This may camouflage the deficits of this subgroup in the perception of facial expressions.

3.1.65. Minshew, N.J., Goldstein, G. **"The pattern of intact and impaired memory functions in autism."** *J Child Psychol Psychiatry* 2001 Nov;42(8):1095-101.

University of Pittsburgh School of Medicine, Pennsylvania, USA. minshewnj@msx.upmc.edu

A battery of tests of auditory and visual memory was used to investigate memory function in 52 high-functioning adolescents and young adults with autism and 40 group-matched normal controls. It was hypothesized that memory dysfunction is present in autism but is not modality specific

and is produced by poor utilization of organizing strategies. It was therefore hypothesized that memory impairment in autism would become more prominent as task complexity was increased. The participants with autism performed as well as controls on short-term memory and paired-associate learning tasks, but performed significantly less well than controls on a list learning task. They also performed significantly more poorly on immediate and delayed recall of a story and of a complex geometric figure. On a maze learning task, their performance became progressively worse relative to controls as the complexity of the maze increased. On a series of span tasks, they did not differ from controls on letter span, but did significantly worse on word span and sentences of increasing complexity. These findings indicate a lack of modality specificity and a failure to initiate organizing strategies as evidenced by inefficiency in new learning, poor utilization of contextual cues in story and complex pattern recall, and greater impairment with increasing complexity of the material.

3.1.66. Ruffman, T., Garnham, W., Rideout, P. **"Social understanding in autism: eye gaze as a measure of core insights."** *J Child Psychol Psychiatry* 2001 Nov;42(8):1083-94.

University of Sussex, Brighton, UK. tedr@biols.susx.ac.uk

Twenty-eight children with autism and 33 MLD children were given two tasks tapping social understanding and a control task tapping probability understanding. For each task there was a measure of eye gaze (where children looked when anticipating the return of a story character or an object) and a verbal measure (a direct question). We found that eye gaze was better than verbal performance at differentiating children with autism from children with MLD. Children with autism did not look to the correct location in anticipation of the story character's return in the social tasks, but they did look to the correct location in the nonsocial probability task. We also found that within the autistic group, children who looked least to the correct location were rated as having the most severe autistic characteristics. Further, we found that whereas verbal performance correlated with general language ability in the autistic group, eye gaze did not. We argue that: (a) eye gaze probably taps unconscious but core insights into social behavior and as such is better than verbal measures at differentiating children with autism from mentally handicapped controls, (b) eye gaze taps either spontaneous processes of simulation or rudimentary pattern recognition, both of which are less based in language, and (c) the social understanding of children with autism is probably based mostly on verbally mediated theories whereas control children also possess more spontaneous insights indexed by eye gaze.

3.1.67. Minshew, N.J., Goldstein, G. **"The pattern of intact and impaired memory functions in autism."** *J Child Psychol Psychiatry* 2001 Nov; 42(8): 1095-101.

University of Pittsburgh School of Medicine, Pennsylvania, USA. minshewnji@msx.upmc.edu

A battery of tests of auditory and visual memory was used to investigate memory function in 52 high-functioning

adolescents and young adults with autism and 40 group-matched normal controls. It was hypothesized that memory dysfunction is present in autism but is not modality specific and is produced by poor utilization of organizing strategies. It was therefore hypothesized that memory impairment in autism would become more prominent as task complexity was increased. The participants with autism performed as well as controls on short-term memory and paired-associate learning tasks, but performed significantly less well than controls on a list learning task. They also performed significantly more poorly on immediate and delayed recall of a story and of a complex geometric figure. On a maze learning task, their performance became progressively worse relative to controls as the complexity of the maze increased. On a series of span tasks, they did not differ from controls on letter span, but did significantly worse on word span and sentences of increasing complexity. These findings indicate a lack of modality specificity and a failure to initiate organizing strategies as evidence by inefficiency in new learning, poor utilization of contextual cues in story and complex pattern recall, and greater impairment with increased complexity of the material.

3.1.68. Ruffman, T., Garnham, W., Rideout, P. **"Social understanding in autism; eye gaze as a measure of core insights."** *J Child psychol psychiatry* 2001 Nov: 42(8);1083-94.

University of Sussex, Brighton, UK. tedr@biols.susx.ac.uk

Twenty-eight children with autism and 33 MLD children were given two tasks tapping social understanding and a control task tapping probability understanding for each task there was a measure of eye gaze (where children looked when anticipating the return of a story character or an object) and a verbal performance at differentiating children with autism from children with MLD. Children with autism did not look to the correct location in anticipation of the story characters return in the social tasks but they did look to the correct location in the nonsocial probability task. We also found that within the autistic group, children who looked least to the correct location were rated as having the most severe autistic characteristics. Further we found that whereas verbal performance correlated with general language ability in the autistic group, eye gaze did not. We argue that: (a) eye gaze probably taps unconscious but core insights into social behaviour and as such is better than verbal measure at differentiating children with autism from mentally handicapped controls, (b) eye gaze taps either spontaneous processes of simulation or rudimentary pattern recognition, both of which are less based in language, and (c) the social understanding of children with autism is probably based mostly on verbally mediated theories whereas control children also possess more spontaneous insights indexed by eye gaze.

3.1.69. Toichi, M., Kamio, Y. **"Verbal association for simple common words in high-functioning autism."** *J Autism Dev Disord* 2001 Oct;31(5) : 483-90.

Division of Child & Adolescent Psychiatric, Case Western Reserve University/University Hospitals of Cleveland, OH 44106, USA.

We investigated conceptual relationships in semantic memory using an indirect priming technique in high-functioning autistic adolescents and their controls who were matched for age, verbal IQ, performance IQ, and nonverbal reasoning ability. The prime was a single word and the target task was completing a word fragment that was semantically related or unrelated to the prime word. The autistic subjects and controls showed similar semantic priming effects, indicating intact conceptual relationships for simple common words in those with autism. Only in the autistic group was a significant correlation found between performance for the related items and two nonverbal cognitive measures, which suggests a possibility that semantic processing in individuals with autism might be qualitatively different from that in controls.

3.1.70. Ruble, L.A. "Analysis of social interactions as goal-directed behaviors in children with autism." *J Autism Dev Disord* 2001 Oct; 31(5) : 471-82.

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An ecological psychology framework that considers the intentions of the child within the child's own social context was used to study the complexity of social interactions of 16 children with autism or Down syndrome. Children were observed in their homes and behaviors were recorded. Records were then analyzed by dividing behavior based on the children's own goals. Goal-directed behaviors were then categorized. Statistical analyses revealed similar social contexts and opportunities to receive bids from other for both groups. Differences in the frequencies and complexities of children's behaviors depended on behavioral intent. Socially intended behaviors were less frequent, less self-initiated, and less complex in children with autism. These findings are discussed as problems of attention and executive function, because social behaviors were more likely to occur secondarily, within the context of another ongoing behavior.

3.1.71. Steinmetz, J.E., Tracy, J.A., Green, J.T. "Classical eyeblink conditioning: clinical models and applications." *Integr Physiol Behav Sci* 2001 Jul-Sep; 36(3):220-38. Publication Types:Review, Review, Tutorial.

Department Psychology, Indiana University, Bloomington 47405, USA steinmet@indiana.edu

In this paper, we argue that the main reason that classical eyeblink conditioning has proven so useful when applied to clinical situations, is that a great deal of information is known about the behavioural and neural correlates of this form of associative learning. Presented here is a summary of three lines of research that have used classical eyeblink conditioning to study three different clinical conditions; autism, fetal alcohol syndrome, and obsessive-compulsive disorder. While seemingly very different clinical conditions, classical eyeblink conditioning has proven very useful for advancing our understanding of these clinical pathologies and the neural conditions that may underlie them.

3.1.72. O'Riordan, M., Plaisted, K. "Enhanced discrimination in autism". *Q J Exp Psychol A* 2001 Nov; 54(4): 961-79.

Department of Experimental Psychology, University of Cambridge, UK. mafo100@cus.cam.ac.uk

Children with autism are superior to typically developing children at visual search tasks (O'Riordan, Plaisted, Driver, & Baron-Cohen, in press; Plaisted, O'Riordan, & Baron-Cohen, 1998b). This study investigates the reasons for this phenomenon. The performance of children with autism and of typically developing children was compared on a series of visual search tasks to investigate two related problems. The first issue was whether the critical determinant of search rate in children is the discriminability of the display items, as it is in normal adults. The second question investigated was whether the superior performance of individuals with autism on visual search tasks is due to an enhanced ability to discriminate between display items. The results demonstrated that discriminability is the rate-determining factor for children with and without autism, replicating earlier findings with normal adults, and that children with autism have an enhanced ability to discriminate between display items. Thus, it seems that an enhanced ability to discriminate between display items underlies superior visual search in autism.

3.1.73. Frith, U. "Mind blindness and the brain in autism." *Neuron* 2001 Dec 20; 32 (6) : 969-79. Publication Types: Review, Review Literature.

UCL Institute of Cognitive Neuroscience, 17 Queen Square, WC1N 3 AR, London, United Kingdom. u.frith@ucl.ac.uk

Experimental evidence shows that the inability to attribute mental states, such as desires and beliefs, to self and others (mentalizing) explains the social and communication impairments of individuals with autism. Brain imaging studies in normal volunteers highlight a circumscribed network that is active during mentalizing and links medial prefrontal regions with posterior superior temporal sulcus and temporal poles. The brain abnormality that results in mentalizing failure in autism may involve weak connections between components of this system.

3.1.74. Craig, J., Baron-Cohen, S., Scott, F. "Drawing ability in autism: a window in to the imagination." *Isr J Psychiatric Relat Sci* 2001 ; 38(3-4):242-53.

Departments of Experimental Psychological and Psychiatry, Autism Research Centre, Downing Street, University of Cambridge, Cambridge, CB3 3EB, England. sb205@cus.cam.ac.uk

This Study investigated imagination via drawing tasks, in 15 children with autism and 15 children with Asperger Syndrome, compared to verbal mental age matched normal children and children with moderate learning difficulties (MLD). Experiment 1 used the Draw an Impossible Man Task. While children with autism were impaired relative to the normal group, they were not impaired relative to the children with MLD. In order to probe for an imagination deficit, Experiment 2 employed a more challenging measures of

imaginative drawing, a task involving mixing categories to produce drawings of real or unreal entities (e.g. drawing half-fish/half-mouse). This revealed an autism-specific deficit. Experiment 3 confirmed this was not due to difficulties in combining elements per se. Experiment 4 required subjects to transform a picture (e.g., a cloud into a swan) and again found an autism-specific deficit. Children with Asperger Syndrome were only impaired when required to make such transformations spontaneously.

3.1.75. Watling, R.L., Deitz, J., White, O. "Comparison of Sensory Profile scores of young children with and without autism spectrum disorders." *Am J Occup Ther* 2001 Jul - Aug; 55(4) : 416-23.

Division of Occupational Therapy, Department of Rehabilitation Medicine, University of Washington, Box 356490, Seattle, Washington 98195, USA. rwaitng@u.washington.edu

OBJECTIVES: The purpose of this study was to describe the sensory-based behaviors of young children with autism as reported by their parents on the Sensory Profile. Factor scores of children with autism were compared with those of children without autism. **METHOD:** The Sensory Profile questionnaire was completed by parents of 40 children with autism 3 through 6 years of age and parents of 40 children without autism was significantly different from that of children without autism on 8 of 10 factors. Factors where differences were found included Sensory Seeking, Emotionally Reactive, Low Endurance/Tone, Oral Sensitivity, Inattention/Distractibility, Poor Registration, Fine Motor / Perceptual, and Other. **CONCLUSION:** Findings from the study suggest that young children with autism have deficits in a variety of sensory processing abilities as measured by the sensory profile. Further research is needed to replicate these findings, to examine the possibility of subgroups on the basis of sensory processing, and to contrast the sensory processing abilities of children with other disabilities to those of children with autism.

3.1.76. Reddy, V., Williams, E., Vaughan, A. "Sharing laughter: the humour of pre-school children with Down syndrome." *Downs Syndr Res Pract* 2001 Oct; 7(3): 125-8.

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Humour and laughter have often been portrayed as fundamentally cultural and social phenomena. They can be used to tell us about children's ability to engage socially and to understand others, but have rarely been explored for this purpose. The present paper summarises the results of a study of simple forms of humour in children with Down syndrome and with autism, two groups which are reported to differ in their sociality and interpersonal understanding. Sixteen children with Down syndrome and 19 children with autism, matched on non-verbal mental age, participated in a cross-sectional study. Parental reports and video-tapes of naturalistic interaction between parents and children were

analysed to show that although there were no overall differences in the presence or frequency of child or parent laughter between the two groups, there were differences in what sorts of events more likely to prompt child laughter, the extent to which child laughter was shared, and how the children responded to other's laughter. The children with Down syndrome were more likely than the children with autism to laugh at funny faces and socially inappropriate acts and less likely to laugh in strange or inexplicable situations, and more likely to laugh shared events. They also responded to other's laughter with attention or smiles more, and tried to re-act it through acts of clowning. Children with Down syndrome are thus active participants in humour and laughter, sharing it at both an emotional and a cultural level.

3.1.77. Gillot, A., Furniss, F., Walter, A. "Anxiety in high-functioning children with autism." *Autism* 2001 Sep;5(3): 277-86.

Department of Learning Disabilities, Highbury Hospital, Bulwell, Nottingham, UK.

High-functioning children with autism were compared with two control groups on measures of anxiety and social worries. Comparison control groups consisted of children with specific language impairment (SLI) and normally developing children. Each group consisted of 15 children between the ages of 8 and 12 years and were matched for age and gender. Children with autism were found to be most anxious on both measures. High anxiety subscale scores for the autism group were separation anxiety and obsessive-compulsive disorder. These findings are discussed within the context of theories of autism and anxiety in the general population of children. Suggestions for future research are made.

3.1.78. Perry, D.W., Marston, G.M., Hinder, S.A., Munden, A.C., Roy, A. "The phenomenology of depressive illness in people with a learning disability and autism." *Autism* 2001 Sep; 5(3): 265-75.

Gulson Road Hospital, Coventry, UK.

People with autism may develop new behaviours in adolescence or early adult life, in addition to those associated with the primary disorder. Some of these behaviours have been postulated to be symptoms of depressive disorder. This article notes the methodological problems of investigating depression in people with autism. The authors also attempt to clarify the symptoms that may be significant in diagnosing depression in this group, by using treatment response methods.

3.1.79. Rinehart, N.J., Bradshaw, J.L., Moss, S.A., Brereton, A.V., Tonge, B.J. "A deficit in shifting attention present in high-functioning autism but not Asperger's disorder." *Autism* 2001 Mar;5(1): 67-80. Erratum in: *Autism* 2002 Mar; 6(1): 141.

Neuropsychology Research Unit, Department of Psychology, Monash University, Clayton, Victoria, Australia. Nicole.Rinehart@sci.monash.edu.au

The aim of this study was to examine executive functioning, in particular, attentional set-shifting deficits in high-functioning autism (n=12) and Asperger's disorder (n=12). A large or global digit composed of smaller or local digits was presented during each trial. The participants indicated the presence of 1s or 2s by pressing the appropriate button. These targets could appear globally or locally. Relative to IQ, sex and age matched controls, reaction time to global targets in this deficiency in shifting from local to global processing, however, was not observed in individuals with Asperger's disorder. The theoretical and neurobiological significance of this dissociation in executive functioning in these clinically related disorders was explored.

3.1.80. Shu, B.C., Lung, F.W., Tien, A.Y., Chen, B.C. "Executive function deficits in non-retarded autistic children." *Autism* 2001 Jun; 5(2): 165-74.

School of Nursing, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

The purpose of this study was to examine differences between Taiwanese children with autism and their typically developing peers on the Wisconsin Card Sorting Test (WCST). Twenty-six children with autism of normal IQ were included, and matched for chronological age with 52 controls. The WCST scores of the typically developing children were significantly higher for categories completed and percent conceptual level than in the autism group. Scores on perseverative responses, perseverative errors, the number of trails to complete the first category and non-perseverative errors were significantly higher in the autism group. The implications of these findings are discussed.

3.1.81. Werth, A., Perkins, M., Boucher, J. "Here's the weavery looming up': verbal humour in a woman with high-functioning autism." *Autism* 2001 Jun; 5(2): 111-25.

Community Health South London NHS Trust, UK.

A case study of Grace, a 29-year-old woman with high-functioning autism, is presented. Grace is unusual for a person with autism in that she produces a great deal of humorous and creative word play. She is also unusual in that she writes and then audio-records letters to her family, and produces copious cartoon-like drawings which she annotates, with the result that multiple examples of her humour are available in permanent form. We present examples of Grace's use of puns, jokes, neologisms, portmanteau words, irreverent humour, irony, sarcasm and word play based on her obsessional interests. The examples are used to illustrate the forms and content of Grace's humour, and are discussed in relation to current theories of autism and of normal humour.

3.1.82. van der Geest, J.N., Kemner, C., Camfferman, G., Verbaten, M.N., van Engeland, H. "Eye movements, visual attention, and autism: a saccadic reaction time study using the gap and overlap paradigm." *Biol Psychiatry* 2001 Oct 15; 50(8): 614-9.

Department of Child and Adolescent Psychiatry, University Medical Centre, Utrecht, The Netherlands.

BACKGROUND: On the basis of the literature on autism, it was hypothesized that children with autism have deficits in attentional (dis-) engagement mechanisms. **METHODS:** A saccadic gap-overlap task was used to study visual engagement and disengagement in 16 high-functioning autistic children of about 10 years of age and 15 age- and IQ-matched normal control children. Subjects were asked to make saccadic eye movements from fixation point to a suddenly appearing target as fast as possible. The saccadic reaction time was compared in two conditions: 1) the overlap condition, in which the fixation point was continuously visible, and 2) the gap condition, in which the fixation point was turned off 200 msec before the target appeared. **RESULTS:** Although no differences between the groups in either condition was observed, the gap effect (i.e., the differences in saccadic reaction time between the overlap condition and the gap condition) was smaller in the autistic group than in the control group. **CONCLUSIONS:** We concluded that autistic children show a lower level of attentional engagement.

3.1.83. Goldstein, G., Beers, S.R., Siegel, D.J., Minshew, N.J. "A comparison of WAIS-R profiles in adults with high-functioning autism or differing subtypes of learning disability." *Appl Neuropsychol* 2001;8(3): 148-54.

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To examine cognitive differences among adults with differing developmental disorders, a comparison of Wechsler Adult Intelligence Scale-Revised profiles was made with samples of 35 individuals with high-functioning autism (HFA) and 102 individuals with adult learning disability (LD). All participants had Verbal and Performance IQ scores of 70 or higher. The LD group was divided into 3 subtypes based on relative achievement levels in mechanical reading and arithmetic. The group with HFA had a profile characterized by a high score on Block Design with low Comprehension score. The HFA group most resembled the LD subtype that had superior achievement in reading relative to arithmetic with the exception of their poor performance on measures of social perception and judgement. Results are discussed in terms of the substantial differences in cognitive structure between these 2 neurodevelopmental disorders and are considered in the context of the learning deficits reported for Asperger's Disorder and non-verbal learning disability.

3.1.84. Hauck, J.A., Dewey, D. "Hand preference and motor functioning in children with autism." *J Autism Dev Disord* 2001 Jun;31(3):265-77.

University of Calgary, Alberta, Canada.

This study examined three theories that have been proposed to explain the high rates of ambiguous hand preference in young children with autism. Twenty children with autism were matched with 20 children with developmental delays and 20 normally developing children. The groups were compared on measures of hand preference and motor skills. Results indicated that the lack of development of a hand preference

in children with autism was not a direct function of their cognitive delay, as the children with developmental delays showed a dissimilar pattern of hand preference. The lack of a definite hand preference in the children with autism was also not due to a lack of motor skill development, as the children with developmental delays displayed similar levels of gross and fine motor skills without the accompanying lack of a definite hand preference. The finding that children with autism with a definite hand preference displayed better performance on motor, language, and cognitive tasks than children with autism who did not display a definite hand preference, however, provided support for the bilateral brain dysfunction hypothesis.

3.1.85. Ozonoff, S., Strayer, D.L. "Further evidence of intact working memory in autism." *J Autism Dev Disord* 2001 Jun;31(3):257-63.

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Earlier investigations have found mixed evidence of working memory impairment in autism. The present study examined working memory in a high-functioning autistic sample, relative to both a clinical control group diagnosed with Tourette Syndrome and a typically developing control group. No group differences were found across three tasks and five dependent measures of working memory. Performance was significantly correlated with both age and IQ. It is concluded that working memory is not one of the executive functions that is seriously impaired in autism. We also suggest that the format of administration of working memory tasks may be important in determining whether or not performance falls in the impaired range.

3.1.86. Soderstrom, H., Blennow, K., Manhem, A., Forsman, A. "CSF studies in violent offenders. I. 5-HIAA as a negative and HVA as a positive predictor of psychopathy." *J Neural Transm* 2001;108(7):869-78.

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Low serotonin activity in man has been related to impulsive, self-destructive violence but not to instrumental aggression aimed at dominance. A relationship has also been suggested between aggression and high catecholaminergic activity. Several studies have reported signs of aberrant dopaminergic function in attention deficit hyperactivity disorder, autism, and schizophrenia. In 22 violent offenders undergoing pretrial forensic psychiatric investigation, interpersonal and behavioral features of psychopathy, measured by the Psychopathy Checklist Revised (PCL-R), were significantly predicted by low cerebrospinal fluid (CSF) concentrations of 5-HIAA and high CSF concentrations of HVA in multivariate regression models. CSF concentrations of MHPG did not contribute to the model. This seems to link the outward-directed aggression of psychopathy to serotonergic hypofunctioning and high dopamine turnover, which might account for disinhibition of destructive impulses.

3.1.87. Dyck, M.J., Ferguson, K., Shochet, I.M. "Do autism spectrum disorders differ from each other and from non-spectrum disorders on emotion recognition tests?" *Eur Child Adolesc Psychiatry* 2001 Jun;10(2):105-16.

School of Psychology, Curtin University of Technology, Perth, Western Australia.

We tested whether dimensional measures of empathic ability, theory of mind, and intelligence would differentiate autism spectrum disorders from each other and from non-spectrum disorders. Tests were administered to children with a diagnosis of Autistic Disorder (AutD; n = 20), Asperger's Disorder (AspD; n = 28), Attention Deficit/Hyperactivity Disorder (Inattentive Type) (ADHD; n = 35), Mental Retardation (Mild) (MR; n = 34), Anxiety Disorder (AnxD; n = 14), or No Psychological Disorder (NPD; n = 36). Results showed that empathic ability discriminated among groups on the autism spectrum (AutD < AspD < NPD). Because empathic ability is not independent of intelligence (AutD < AspD < NPD on intelligence; MR < ADHD < NPD on empathic ability), both dimensions are necessary to discriminate autism spectrum from non-spectrum disorders. When intelligence is covaried, empathic ability discriminated AutD, but not AspD, from other disorders (AutD < MR < ADHD < NPD = AnxD = AspD).

3.1.88. Yamamoto, J.I., Kakutani, A., Terada, M. "Establishing joint visual attention and pointing in autistic children with no functional language." *Percept Mot Skills* 2001 Jun;92(3 Pt 1):755-70.

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Joint visual attention is defined as looking where someone else is looking. The purpose of this study was to examine the conditions for establishing joint visual attention in autistic children who have no functional speech. An experimenter, sitting facing the child, looked at one of six pictures near the child. Analysis showed that joint visual attention to stimuli behind the child and therefore outside of the visual field occurred at a higher rate when the visual angle between the stimuli was about 60 degrees. Spontaneous pointing at the target object increased with training which included feedback and physical guidance. These results are discussed in terms of the effects of environmental variables and perceptual mechanisms on the emergence of joint visual attention in autistic children. The possibility of using an adult's social cues and expanding the child's visual field as a remedial procedure is also addressed.

3.1.89. Liss, M., Harel, B., Fein, D., Allen, D., Dunn, M., Feinstein, C., Morris, R., Waterhouse, L., Rapin, I. "Predictors and correlates of adaptive functioning in children with developmental disorders." *J Autism Dev Disord* 2001 Apr;31(2):219-30.

University of Connecticut, Storrs, USA.

Autism is a developmental disorder marked by impairments in socialization, communication, and perseverative behavior

and is associated with cognitive impairment and deficits in adaptive functioning. Research has consistently demonstrated that children with autism have deficits in adaptive functioning more severe than their cognitive deficits. This study investigates the correlates and predictors of adaptive functioning as measured by the Vineland Adaptive Behavior Scales in high- and low-functioning children with autism and their age and nonverbal IQ matched controls. Thirty-five 9-year-old children with high-functioning autism (HAD) were compared with 31 age-matched children with developmental language disorder (DLD), and 40 9-year-old children with low-functioning autism (LAD) were compared with 17 age-matched children with low IQ on adaptive functioning, IQ, autistic symptomology, and tests of language and verbal memory. Results indicate that both groups with autism were significantly impaired compared to their matched controls on Socialization and Daily Living, but not Communication and that these impairments were more pronounced in the HAD group than in the LAD group. Adaptive behavior was strongly correlated with autistic symptomology only in the HAD group. Regression analyses indicated that IQ was strongly predictive of adaptive behavior in both low-functioning groups, but tests of language and verbal memory predicted adaptive behavior in the higher functioning groups. Results suggest that IQ may act as a limiting factor for lower functioning children but higher functioning children are impaired by specific deficits, including autistic symptomology and impaired language and verbal memory.

3.1.90. Travis, L., Sigman, M., Ruskin, E. "Links between social understanding and social behavior in verbally able children with autism." *J Autism Dev Disord* 2001 Apr;31(2):119-30.

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This study investigated the relations between various measures of social understanding and social interaction competence in verbally able children with autism. Measures of social understanding included measures of verbalizable knowledge (false belief understanding, affective perspective taking), as well as measures of more intuitive forms of social responsiveness (empathy, concern to distress, and initiating joint attention). Two measures of social interaction competence were employed: level of engagement with peers on the playground, and prosocial behavior in a structured laboratory task. For children with autism, initiating joint attention and empathy were strongly related to both measures of social interaction competence. No understanding-behavior links were identified for a language-age matched comparison sample of developmentally delayed children. Several accounts of these understanding-behavior links are considered, including the possibility that for children with autism, more impaired forms of understanding are more closely linked to behavior because they serve as limits on competence.

3.1.91. Williams, J.H., Whiten, A., Suddendorf, T., Perrett, D.I. "Imitation, mirror neurons and autism." *Neurosci Biobehav Rev* 2001 Jun;25(4):287-95.

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Various deficits in the cognitive functioning of people with autism have been documented in recent years but these provide only partial explanations for the condition. We focus instead on an imitative disturbance involving difficulties both in copying actions and in inhibiting more stereotyped mimicking, such as echolalia. A candidate for the neural basis of this disturbance may be found in a recently discovered class of neurons in frontal cortex, 'mirror neurons' (MNs). These neurons show activity in relation both to specific actions performed by self and matching actions performed by others, providing a potential bridge between minds. MN systems exist in primates without imitative and 'theory of mind' abilities and we suggest that in order for them to have become utilized to perform social cognitive functions, sophisticated cortical neuronal systems have evolved in which MNs function as key elements. Early developmental failures of MN systems are likely to result in a consequent cascade of developmental impairments characterised by the clinical syndrome of autism.

3.1.92. Beversdorf, D.Q., Anderson, J.M., Manning, S.E., Anderson, S.L., Nordgren, R.E., Felopulos, G.J., Bauman, M.L. "Brief report: macrographia in high-functioning adults with autism spectrum disorder." *J Autism Dev Disord* 2001 Feb;31(1):97-101.

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The initial description of Asperger syndrome commented on the poor handwriting and motor coordination difficulties of individuals with this condition. Early descriptions of autism do not remark upon such difficulties. Recent evidence, however, suggests that individuals with both conditions have a similar motor control impairment. Handwriting has not been formally assessed in this context. Our study compared handwriting size between individuals with autism spectrum disorder and age- and IQ-matched control subjects. Macrographia was observed among subjects with autism spectrum disorder which remained statistically significant when covaried with educational level. This finding may correlate with the anatomical abnormalities present in the cerebellum of individuals with autism spectrum disorder.

3.1.93. Rinehart, N.J., Bradshaw, J.L., Brereton, A.V., Tonge, B.J. "Movement preparation in high-functioning autism and Asperger disorder: a serial choice reaction time task involving motor reprogramming." *J Autism Dev Disord* 2001 Feb;31(1):79-88.

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Autism and Asperger disorder have long been associated with movement abnormalities, although the neurobehavioural details of these abnormalities remain poorly defined. Clumsiness has traditionally been associated with Asperger

disorder but not autism, although this is controversial. Others have suggested that both groups demonstrate a similar global motor delay. In this study we aimed to determine whether movement preparation or movement execution was atypical in these disorders and to describe any differences between autism and Asperger disorder. A simple motor reprogramming task was employed. The results indicated that individuals with autism and Asperger disorder have atypical movement preparation with an intact ability to execute movement. An atypical deficit in motor preparation was found in Asperger disorder, whereas movement preparation was characterized by a "lack of anticipation" in autism. The differences in movement preparation profiles in these disorders were suggested to reflect differential involvement of the fronto-striatal region, in particular the supplementary motor area and anterior cingulate.

3.1.94. Williams, E., Reddy, V., Costall, A. "Taking a closer look at functional play in children with autism." *J Autism Dev Disord* 2001 Feb;31(1):67-77.

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Research evidence indicates that children with autism may experience problems with functional play, in addition to their well-documented deficits in symbolic play. However, as a result of the tendency of previous studies to group all functional play into a single category, the precise nature and extent of this deficit remains unclear. The present study undertook a more refined analysis of such play, subtyping the functional acts into various categories, in terms of the developmental progression suggested by research with typical infants. The functional play of children with autism was compared to that of developmentally matched children with Down syndrome and typical infants. Although there were no group differences in overall measures of the proportion of total play time spent in functional play and in the number of functional acts performed, a closer analysis of the composition of this play did reveal striking, qualitative differences. The functional play of the autism group was less elaborated, less varied, and less integrated than that of the controls. The implications of these findings are explored in relation to current theoretical models of autism and in relation to the role of other people in mediating the appropriate use of objects.

3.1.95. Teunisse, J.P., Cools, A.R., van Spaendonck, K.P., Aerts, F.H., Berger, H.J. "Cognitive styles in high-functioning adolescents with autistic disorder." *J Autism Dev Disord* 2001 Feb;31(1):55-66.

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This study addressed the operationalization, the identification, and the prevalence of weak central coherence and poor cognitive shifting in 35 high-functioning adolescents with autism. Central coherence and cognitive shifting were represented by two factors in a factor analysis, each reflecting a constituent aspect of the domain in question. With regard

to central coherence, these aspects were the ability of piecemeal processing and the ability to process meaning. The aspects related to cognitive shifting concerned internally and externally controlled shifting. Weak central coherence and poor cognitive shifting did not appear to be related to measures of symptom severity, social understanding, and social competence. Both these cognitive styles did not appear to be universal to autism. In our sample, weak central coherence and poor cognitive shifting were found to be significantly more common than in normative control subjects.

3.1.96. Gepner, B., Deruelle, C., Grynfeldt, S. "Motion and emotion: a novel approach to the study of face processing by young autistic children." *J Autism Dev Disord* 2001 Feb;31(1):37-45.

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The specificity of facial processing impairment in autistic children, particularly in the domain of emotion, is still debated. The aim of our study was to assess the influence of motion on facial expression recognition in young autistic children. Thirteen autistic children (M age: 69.38 months) were matched for gender and developmental level with a control group of 13 normal children (M age: 40.53 months). They were compared on their ability to match videotaped "still," "dynamic," and "strobe" emotional and nonemotional facial expressions with photographs. Results indicate that children with autism do not perform significantly worse than their controls in any of our experimental conditions. Compared to previous studies showing lower performance in autistic than in control children when presented with static faces, our data suggest that slow dynamic presentations facilitate facial expression recognition by autistic children. This result could be of interest to parents and specialists involved in education and reeducation of these children.

3.1.97. Kleinman, J., Marciano, P.L., Ault, R.L. "Advanced theory of mind in high-functioning adults with autism." *J Autism Dev Disord* 2001 Feb;31(1):29-36.

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Twenty-four high-functioning adults with autism (16 men) who passed a first-order theory-of-mind task and 24 nonautistic adults (10 men) attributed mental states to recordings of various verbal intonations and to photos of people's eyes to assess advanced theory of mind. Participants with autism performed significantly worse than nonautistic participants on both tasks. Thus, the previously described inattention to others' eyes exhibited by adults with autism is not solely responsible for their inability to attribute mental states from eyes, as they also did not correctly attribute mental states from voices. These findings support the view that a core deficit for people with autism lies in their theory of mind, that is, their inability to attribute mental states to others.

3.1.98. O'Riordan, M.A., Plaisted, K.C., Driver, J., Baron-Cohen, S. "Superior visual search in autism." *J Exp Psychol Hum Percept Perform* 2001 Jun;27(3):719-30.

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Children with a diagnosis of autism and normally developing children, matched for age and general ability, were tested on a series of visual search tasks in 2 separate experiments. The children with autism performed better than the normally developing children on difficult visual search tasks. This result occurred regardless of whether the target was uniquely defined by a single feature or a conjunction of features, as long as ceiling effects did not mask the difference. Superior visual search performance in autism can be seen as analogous to other reports of enhanced unique item detection in autism. Unique item detection in autism is discussed in the light of mechanisms proposed to be involved in normal visual search performance.

3.1.99. Ropar, D., Mitchell, P. "Susceptibility to illusions and performance on visuospatial tasks in individuals with autism." *J Child Psychol Psychiatry* 2001 May;42(4):539-49.

School of Psychology, University of Nottingham, UK.

The current study follows a recent paper reporting that individuals with autism were just as susceptible to visual illusions as those without autism (Ropar & Mitchell, 1999). The possibility that individual differences may account for the failure to replicate Happe's (1996) findings is explored by presenting a battery of visuospatial tasks thought to measure weak central coherence (embedded figures, block design, Rey complex figure test). Participants with autism were distinguished by relatively good performance on visuospatial tasks, though there was no superiority effect in those with Asperger's syndrome. Performance on the visuospatial battery did not significantly predict susceptibility to illusions in various participant groups, including those with autism and Asperger's syndrome. This suggests that perception of illusions and performance on visuospatial tasks may rely on different mechanisms. The implications for the theory of weak central coherence are discussed.

3.1.100. Biro, S., Russell, J. "The execution of arbitrary procedures by children with autism." *Dev Psychopathol* 2001 Winter;13(1):97-110.

Department of Experimental Psychology, University of Cambridge, UK.

Executive tasks typically contain a prepotent lure. In addition, they require individuals either to (a) follow arbitrary procedures or (b) update their model of the physical world. Recent research suggests that children with autism may be challenged only by executive tasks of the former kind (containing arbitrary rules). We asked whether this continues to be true when there is no prepotent lure, comparing performance on (a) a task with arbitrariness but without prepotency with (b) a task with both features and (c) a task with neither. The participants with autism performed at a lower level than comparison groups on the first and second task but not on the third task. This outcome is consistent with

the view that autism is associated with difficulties in following arbitrary procedures per se. We try to locate difficulties with acting on the basis arbitrary rules in relation to more mainstream ideas about autistic executive dysfunction.

3.1.101. Klinger, L.G., Dawson, G. "Prototype formation in autism." *Dev Psychopathol* 2001 Winter;13(1):111-24.

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Individuals with autism have difficulty integrating information and generalizing previously learned concepts to new situations. It was hypothesized that these problems result from an underlying impairment in category formation. Persons with autism may not abstract a summary representation (a prototype) during category learning and, instead, may form categories by memorizing a list of rules. Children with autism, Down syndrome, and normal development participated in one set of category learning tasks that could be solved using a rule-based approach and a second set of tasks in which there was no rule that defined category membership (prototype tasks). In the rule-based tasks, all groups were successful at using a rule to learn a new category. In the prototype tasks, only the typically developing children were able to learn a new category. Neither the persons with autism nor the persons with Down syndrome appeared to develop a prototype during category learning. These data suggest that persons with autism and Down syndrome have difficulty categorizing new information by forming prototypes and, instead, tend to rely on a rule-based approach to learning.

3.1.102. Russell, J., Hill, E.L. "Action-monitoring and intention reporting in children with autism." *J Child Psychol Psychiatry* 2001 Mar;42(3):317-28.

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The "mindblindness" theory of core cognitive impairment in autism and at least one of the executive theories of the core cognitive deficit both predict that children with autism should find it difficult to report what their intention was when it diverged from an outcome. The former predicts this because it takes intention reporting to require a "theory of mind" and the latter predicts it because the theory posits an impairment in the monitoring of goal-directed actions. The latter also predicts impairments in the ability to monitor basic actions. Our three studies failed to support either of these views. Experiment 1 demonstrated intact abilities in the monitoring of basic actions (detecting which stimulus of a number of stimuli one is controlling). Experiment 2 demonstrated intact abilities in reporting an intention, both for self and for another agent, when the outcome was unintended but desired. In Experiment 3, using the novel "transparent intentions task", we found (with a minor qualification) intact ability in reporting on nonballistic intended actions when the result that the action achieved was unexpected. The implications of these results for views of the relation between theory of mind and executive difficulties in autism are discussed.

3.1.103. Maestro, S., Muratori, F., Barbieri, F., Casella, C., Cattaneo, V., Cavallaro, M.C., Cesari, A., Milone, A., Rizzo, L., Viglione, V., Stern, D.D., Palacio-Espasa, F. "Early behavioral development in autistic children: the first 2 years of life through home movies." *Psychopathology* 2001 May-Jun;34(3):147-52.

Scientific Institute Stella Maris, Division of Child Neuropsychiatry, University of Pisa, Italy.

OBJECTIVE: The main aim of the research is to study the early behavioral development in autistic children through home movies. **METHODS:** fifteen home movies, regarding the first 2 years of life of autistic children are compared with the home movies of 15 normal children. The films of the two groups were mixed and rated by blind ratings with the Grid for the Assessment of Normal Behavior in Infants and Toddlers. The grid is composed of 17 items grouped into three developmental areas: social competence, intersubjectivity and symbolic activity. For every area, we have identified specific children's behaviors. **RESULTS:** Significant differences between the two groups are found both in the range of age 0-6 for intersubjectivity, and in the ranges of age 6-12 and 18-24 for symbolic activity. **CONCLUSIONS:** The authors pose some hypotheses about an early-appearing impairment of intersubjectivity, the ability to represent other's state of mind, in subjects with autistic disorder. Copyright 2001 S. Karger AG, Basel

3.1.104. Noterdaeme, M., Amorosa, H., Mildenerger, K., Sitter, S., Minow, F. "Evaluation of attention problems in children with autism and children with a specific language disorder." *Eur Child Adolesc Psychiatry* 2001 Mar;10(1):58-66.

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Children with autism and children with a specific language disorder show additional attention deficits. The literature on the neuropsychological investigation of attention in both groups of children suggests that the nature of their attention problems might be different. The purpose of this study is to examine the attention test profiles in these two groups of children with developmental disorders. Nineteen children and adolescents with autism, 17 subjects with a specific language disorder and 19 control subjects participated in the study. Non-verbal intelligence was normal for all subjects. The "Testbatterie zur Aufmerksamkeitsprüfung" was administered to all subjects. This instrument provides the possibility to examine a wide range of attention functions and executive functions. The results showed that the autistic individuals had deficits in executive functions, whereas the language impaired children had deficits in auditory sustained attention, in auditory selective attention, and in the domain of executive functions. It is concluded that although both groups of developmentally impaired subjects showed attention problems, the deficits are not the same in both groups. The different neuropsychological profiles probably reflect different mechanisms in the pathogenesis of the attention deficits in both types of developmental disorders.

3.1.105. Pierce, K., Courchesne, E. "Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism." *Biol Psychiatry* 2001 Apr 15;49(8):655-64.

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BACKGROUND: Although limited environmental exploration in autism is an obvious behavioral feature and may be a manifestation of "restricted interests" as described in DSM-IV criteria, there have been no behavioral or neurobiological studies of this important aspect of the disorder. Given consistent reports of cerebellar abnormality in autism, combined with animal research showing a relationship between exploration and the cerebellum, this study aimed to test the possible link between cerebellar abnormality and exploration in autism. **METHODS:** The relationship between visuospatial exploration, stereotyped motor movements, and magnetic resonance imaging measures of the cerebellar vermis, whole brain volume, and frontal lobes in 14 autistic and 14 normal children was investigated. Children were exposed to a large room with several exploration containers and instructed to play. Exploration behavior was videotaped and scored for percentage of time engaged in exploration, number of containers explored, as well as stereotyped movements. **RESULTS:** Children with autism spent significantly less time in active exploration and explored fewer containers overall than normal children. Measures of decreased exploration were significantly correlated with the magnitude of cerebellar hypoplasia of vermal lobules VI-VII in the autistic children, but no relationship to vermis size was found with normal control children. Further, measures of rates of stereotyped behavior were significantly negatively correlated with area measures of cerebellar vermis lobules VI-VII and positively correlated with frontal lobe volume in the autism sample. **CONCLUSIONS:** Reduced environmental exploration and repetitive behavior may have particularly important developmental consequences for children with autism because it may lead them to miss learning opportunities that fall outside their scope of interest. Our findings represent the first documented link between the restricted range of interests and stereotyped behaviors pathognomonic of autism and particular neuroanatomic sites.

3.1.106. Jaffe, J.S., Timell, A.M., Gulanski, B.I. "Prevalence of low bone density in women with developmental disabilities." *J Clin Densitom* 2001 Spring;4(1):25-9.

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This study was designed to assess the prevalence and severity of low bone mineral density in an institutionalized population of postmenopausal women (n = 79) with developmental disabilities, using quantitative ultrasound of the calcaneus. The results demonstrate that this population has a significantly lower quantitative ultrasound index (QUI) of the calcaneus compared with a referent population of age-matched control subjects without mental disabilities. We used

the QUI T-score threshold of <-2.0 standard deviations (SDs) to define individuals at high risk for osteoporosis, and 82% of the study participants met this criterion. Furthermore, approx 43% of the population had a heel QUI that was more than 2 SDs below that of age-matched control subjects, consistent with a severe degree of demineralization.

3.1.107. Dunn, M.E., Burbine, T., Bowers, C.A., Tantleff-Dunn, S. "Moderators of stress in parents of children with autism." *Community Ment Health J* 2001 Feb;37(1):39-52.

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Parents of children with autism experience more stress and are more susceptible to negative outcomes than parents of children with other disabilities. The present work examines the relationship between stressors, social support, locus of control, coping styles, and negative outcomes (depression, social isolation, and spousal relationship problems) among parents of children with autism. Fifty-eight parents completed surveys. Results indicated that several coping styles corresponded to negative outcomes. Furthermore, the relationship between stressors and negative outcomes was moderated by social support and coping style. Results are discussed in relation to applications for clinical practice.

3.1.108. Roeyers, H., Buysse, A., Ponnet, K., Pichal, B. "Advancing advanced mind-reading tests: empathic accuracy in adults with a pervasive developmental disorder." *J Child Psychol Psychiatry* 2001 Feb;42(2):271-8.

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Research using advanced but static mind-reading tests with high-functioning adults with a pervasive developmental disorder (PDD) provided evidence for subtle social cognitive deficits. In the present study, adults with PDD were unimpaired on such tasks, relative to individually matched normal controls. Significant differences between the two groups were, however, found on a more naturalistic empathic accuracy task developed for this study. Participants viewed two videotaped interactions that both depicted a male and female stranger having an initial conversation and were asked to infer the unexpressed thoughts and feelings of the four targets. Subjects with PDD performed significantly worse on the second video. These findings suggest that the mind-reading deficit of a subgroup of able adults with PDD may only be apparent when a sufficiently complex naturalistic assessment method is being used.

3.1.109. Liss, M., Fein, D., Allen, D., Dunn, M., Feinstein, C., Morris, R., Waterhouse, L., Rapin, I. "Executive functioning in high-functioning children with autism." *J Child Psychol Psychiatry* 2001 Feb;42(2):261-70.

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Executive functioning was investigated in 34 children (24 boys and 10 girls) with developmental language disorder (DLD)

and 21 children (18 boys and 3 girls) with high-functioning autistic disorder (HAD) matched on Full Scale IQ, Nonverbal IQ, age (mean age 9 year, 1 month), and SES. The DLD group had a Verbal IQ that was 10 points higher than the HAD group. These children were given the Wisconsin Card Sorting Test (WCST), the Mazes subtest from the WISC-R, the Underlining test, and the Rapid Automatized Naming test. In addition, these children were given the Vineland Scales of Adaptive Functioning and the Wing Diagnostic Symptom Checklist in order to assess severity of autistic symptomatology. Results indicated that the only significant difference between the two groups on the cognitive tasks was perseverative errors on the WCST; there was no significant difference on total number of categories achieved or total number of errors on the WCST or on the other executive function measures. There was also significant overlap in the scores between the two groups and the difference in perseverative errors was no longer significant when Verbal IQ was partialled out. Executive functioning was strongly related to all IQ variables in the DLD group and particularly related to Verbal IQ in the HAD group. Although there was a relationship in the HAD group between executive functioning and adaptive functioning, as well as between executive functioning and autistic symptomatology, these relationships were generally no longer significant in the HAD group after the variance due to Verbal IQ was accounted for. The results are interpreted to indicate that although impaired executive functioning is a commonly associated feature of autism, it is not universal in autism and is unlikely to cause autistic behaviors or deficits in adaptive function.

3.1.110. Mottron, L., Morasse, K., Belleville, S. "A study of memory functioning in individuals with autism." *J Child Psychol Psychiatry* 2001 Feb;42(2):253-60.

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Memory tasks were administered to 14 high-functioning individuals with autism and 14 typically developing individuals matched on chronological age and verbal intelligence. The tasks consisted of free and cued recall of 15 semantically unrelated words in 3 encoding conditions: phonological encoding, semantic encoding, and a no encoding orientation. In both groups, semantic orientation led to better free recall than did orientation toward syllabic encoding or absence of orientation. In contrast, semantic cues at retrieval led to better cued recall than phonological cues in typically developing individuals, whereas both types of cue had the same effect in prompting cued recall for individuals with autism. These findings are incompatible with the hypothesis of an amnesic deficit and do not support the notion of executive or semantic deficits in the memory problems of autistic individuals, at least for those with a high level of functioning. It is proposed that these findings can be accounted for by enhanced phonological processing in autism. This interpretation is consistent with other findings of enhanced processing of low-level perceptual information in the visual and auditory modality in autism.

3.1.111. Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I. "The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism." *J Child Psychol Psychiatry* 2001 Feb;42(2):241-51. Publication Types: Validation Studies.

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In 1997 in this Journal we published the "Reading the Mind in the Eyes" Test, as a measure of adult "mentalising". Whilst that test succeeded in discriminating a group of adults with Asperger syndrome (AS) or high-functioning autism (HFA) from controls, it suffered from several psychometric problems. In this paper these limitations are rectified by revising the test. The Revised Eyes Test was administered to a group of adults with AS or HFA (N = 15) and again discriminated these from a large number of normal controls (N = 239) drawn from different samples. In both the clinical and control groups the Eyes Test was inversely correlated with the Autism Spectrum Quotient (the AQ), a measure of autistic traits in adults of normal intelligence. The Revised Eyes Test has improved power to detect subtle individual differences in social sensitivity.

3.1.112. Gilchrist, A., Green, J., Cox, A., Burton, D., Rutter, M., Le Couteur, A. "Development and current functioning in adolescents with Asperger syndrome: a comparative study." *J Child Psychol Psychiatry* 2001 Feb;42(2):227-40.

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Adolescents with Asperger syndrome (AS: without delay in speech development, diagnosed according to ICD-10 clinical criteria) were compared with a group with high-functioning autism (HFA: all with delayed speech development), and a group with conduct disorder (CD). Family and genetic studies suggest that Asperger syndrome and autism form part of the same spectrum, whereas the social impairments in conduct disorder are assumed to have different origins. The aims were to explore the relationships between early speech development and other aspects of functioning in autistic disorders, and to compare autistic and nonautistic social impairments. Early and current behaviour and IQ profiles were investigated. The CD group were clearly different from both the AS and HFA groups. The AS group tended to have less severe early behavioural abnormalities than the HFA group, and were unlikely to have speech abnormalities, but other communicative, social, and restricted/ stereotyped behavioural difficulties were largely of a similar pattern to the abnormalities in the HFA group. Eighty per cent of the AS group met criteria for autism on the diagnostic algorithm associated with the Autism Diagnostic Interview-Revised. By adolescence, the AS group were reported to be as abnormal as the HFA group but in structured 1:1 interaction their conversation was better. IQ profile in the AS group showed relative strength on verbal measures, unlike the HFA group, but relatively good performance on the Block Design subtest of the WISC/WAIS was a feature of both the AS and HFA

groups. The results indicate closely similar behavioural manifestations may arise by adolescence despite differences in speech development. Follow-up studies and further family investigations will be required to clarify the origins of these and other patterns of autistic development.

3.1.113. Adolphs, R., Sears, L., Piven, J. "Abnormal processing of social information from faces in autism." *J Cogn Neurosci* 2001 Feb 15;13(2):232-40.

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Autism has been thought to be characterized, in part, by dysfunction in emotional and social cognition, but the pathology of the underlying processes and their neural substrates remain poorly understood. Several studies have hypothesized that abnormal amygdala function may account for some of the impairments seen in autism, specifically, impaired recognition of socially relevant information from faces. We explored this issue in eight high-functioning subjects with autism in four experiments that assessed recognition of emotional and social information, primarily from faces. All tasks used were identical to those previously used in studies of subjects with bilateral amygdala damage, permitting direct comparisons. All subjects with autism made abnormal social judgments regarding the trustworthiness of faces; however, all were able to make normal social judgments from lexical stimuli, and all had a normal ability to perceptually discriminate the stimuli. Overall, these data from subjects with autism show some parallels to those from neurological subjects with focal amygdala damage. We suggest that amygdala dysfunction in autism might contribute to an impaired ability to link visual perception of socially relevant stimuli with retrieval of social knowledge and with elicitation of social behavior.

3.1.114. Pickup, G.J., Frith, C.D. "Theory of mind impairments in schizophrenia: symptomatology, severity and specificity." *Psychol Med* 2001 Feb;31(2):207-20.

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BACKGROUND: Several studies have examined the ability of schizophrenic patients to represent mental states ('theory of mind': ToM). There is consensus that some patients have impaired ToM, but there is disagreement about the relation between ToM and symptomatology, and about the severity and specificity of the deficit. METHODS: Two first-order and one second-order false belief tests of ToM were given to groups of schizophrenic patients and psychiatric and normal controls. The relation between ToM and symptomatology was explored using regression and symptom subgroup analyses. Severity was investigated by using the same task methodology as in autism research, to enable direct comparison with that disorder. Specificity was investigated using matched control tasks which were as difficult as the ToM tasks, but did not require ToM. RESULTS: Symptom subgroup analysis showed that schizophrenic patients with behavioural signs were

impaired relative to controls on ToM, and that remitted patients and a single case with passivity symptoms performed as well as controls. Regression analysis showed that ratings of behavioural signs predicted impaired ToM in schizophrenia. There was weak evidence that a subgroup with paranoid symptoms had ToM impairments, although these were associated with low IQ. Schizophrenic patients only showed ToM deficits on the second-order task. No impairments appeared on the matched control tasks which did not require ToM. **CONCLUSIONS:** There is a clear association between ToM impairment and behavioural signs in schizophrenia. Deficits in paranoid patients are harder to detect with current tasks and may be compensated for by IQ-dependent problem-solving skills. ToM impairments in schizophrenia are less severe than in autism, but are specific and not a reflection of general cognitive deficits.

3.1.115. Tierney, E., Nwokoro, N.A., Porter, F.D., Freund, L.S., Ghuman, J.K., Kelley, R.I. "Behavior phenotype in the RSH/Smith-Lemli-Opitz syndrome." *Am J Med Genet* 2001 Jan 15;98(2):191-200.

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The behavior phenotype of Smith-Lemli-Opitz syndrome (SLOS) was studied by assessing behavior, social, and communication abilities, sensory hyperreactivity, and the deficits associated with autistic disorder. Fifty-six SLOS subjects, age 0.3 to 32.3 years, were evaluated by multiple age-dependent questionnaires and telephone interviews. Of the 56 subjects, 50 (89%) had a history of repeated self-injury: 30 (54%) bit themselves; 27 (48%) head-banged; and 30 (54%) threw themselves backward in a highly characteristic upper body movement ("opisthokinesis"). Forty-seven of these subjects were also evaluated by direct observation and by direct interview of the parent or caregiver. Of 11 subjects 10 years or older, three (27%) had a stereotypic stretching motion of the upper body accompanied by hand flicking. Additional measures showed sensory hyperreactivity, temperament dysregulation, sleep disturbance, and social and communication deficits. Nine of 17 subjects (53%) met the diagnostic criteria for autistic disorder by the Autism Diagnostic Interview-Revised (ADI-R) algorithm questions [Lord et al., 1993, 1994]. Thus, SLOS is a metabolic disorder that can be associated with autism and other behavioral characteristics that define a distinctive and diagnostically important behavioral disorder. Copyright 2001 Wiley-Liss, Inc.

3.1.116. Allen, G., Courchesne, E. "Attention function and dysfunction in autism." *Front Biosci* 2001 Feb 1;6:D105-19. Publication Types: Review, Review, Tutorial.

Department of Psychology, San Diego State University, Department of Psychiatry, School of Medicine, University of California, San Diego, USA.

Impairments of attention are among the most consistently reported cognitive deficits in autism, and they continue to be

a key focus of research. This is in no doubt due to the importance of normal attention function to the development of many so-called "higher level" cognitive operations, and to the likely involvement of attention dysfunction in certain clinical features of autism. Autistic individuals display a wide range of attentional abilities and deficits across the many domains of attention function, including selective, sustained, spatial, and shifting attention operations. This unique pattern of attention function and dysfunction has profound implications for the development and treatment of autistic children. The present review will explore this pattern of attentional strengths and weaknesses and the neural defects that underlie them.

3.1.117. McComas, J., Hoch, H., Paone, D., El-Roy, D. "Escape behavior during academic tasks: a preliminary analysis of idiosyncratic establishing operations." *J Appl Behav Anal* 2000 Winter;33(4):479-93.

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The presence or absence of idiosyncratic stimuli has been demonstrated to predictably alter the occurrence of problem behavior. By specifying stimuli related to negatively reinforced behavior during academic tasks, it may be possible to identify methods of instruction that decrease the occurrence of problem behavior. The current study used a four-step procedure that involved a functional analysis, descriptive assessment, establishing operations (EO) analysis, and follow-up evaluation (a) to identify the operant function of destructive behavior and (b) to evaluate the effects of idiosyncratic features of academic task demands and related methods of instruction on the occurrence of negatively reinforced destructive behavior of 3 boys with developmental disabilities and autism in a classroom setting. The data suggest that the four-step procedure was effective in identifying methods of instruction that decreased the likelihood of destructive behavior without disrupting the maintaining contingencies for destructive behavior. Results are discussed in terms of establishing operations for negatively reinforced destructive behavior during academic tasks and related methods of instruction in classroom settings.

3.1.118. Caplan, R., Austin, J.K. "Behavioral aspects of epilepsy in children with mental retardation." *Ment Retard Dev Disabil Res Rev* 2000;6(4):293-9.

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Epilepsy and mental retardation, two relatively common childhood conditions, are both associated with a wide range of behavioral disorders. This article reviews the behavioral disturbances found in children with epilepsy, mental retardation, and both conditions. The behavioral disturbances found in children with epilepsy are associated with seizure-related, cognitive, developmental, and psychosocial factors. Although children with mental retardation also demonstrate a broad spectrum of behavioral disturbances, children with specific mental retardation syndromes have better-defined patterns of psychopathology. The presence of epilepsy and

mental retardation seems to increase the severity of psychopathology. Further studies are needed, however, to define better the interaction of these two conditions and how they impact the behavior of children.

3.1.119. Mostofsky, S.H., Goldberg, M.C., Landa, R.J., Denckla, M.B. "Evidence for a deficit in procedural learning in children and adolescents with autism: implications for cerebellar contribution." *J Int Neuropsychol Soc* 2000 Nov;6(7):752-9.

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To examine the hypothesis that abnormalities in those cognitive functions for which cerebellar components have been implicated contribute to the pathophysiology of autism, tests of judgment of explicit time intervals and procedural learning were administered to 11 participants with autism and 17 age- and IQ-matched controls. Results indicated that the group with autism demonstrated significant impairments in procedural learning compared with the group of controls. No significant difference in judgment of explicit time intervals was found. The data suggest that deficits in procedural learning may contribute to the cognitive and behavioral phenotype of autism; these deficits may be secondary to abnormalities in cerebellar-frontal circuitry.

3.1.120. Mottron, L., Peretz, I., Menard, E. "Local and global processing of music in high-functioning persons with autism: beyond central coherence?" *J Child Psychol Psychiatry* 2000 Nov;41(8):1057-65.

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A multi-modal abnormality in the integration of parts and whole has been proposed to account for a bias toward local stimuli in individuals with autism (Frith, 1989; Mottron & Belleville, 1993). In the current experiment, we examined the utility of hierarchical models in characterising musical information processing in autistic individuals. Participants were 13 high-functioning individuals with autism and 13 individuals of normal intelligence matched on chronological age, nonverbal IQ, and laterality, and without musical experience. The task consisted of same-different judgements of pairs of melodies. Differential local and global processing was assessed by manipulating the level, local or global, at which modifications occurred. No deficit was found in the two measures of global processing. In contrast, the clinical group performed better than the comparison group in the detection of change in nontransposed, contour-preserved melodies that tap local processing. These findings confirm the existence of a "local bias" in music perception in individuals with autism, but challenge the notion that it is accounted for by a deficit in global music processing. The present study suggests that enhanced processing of elementary physical properties of incoming stimuli, as found previously in the visual modality, may also exist in the auditory modality.

3.1.121. Nyden, A., Hjelmquist, E., Gillberg, C. "Autism spectrum and attention-deficit disorders in girls. Some neuropsychological aspects." *Eur Child Adolesc Psychiatry* 2000 Sep;9(3):180-5.

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This study compared the neuropsychological test profiles of non-mentally retarded girls and boys consecutively referred to a neuropsychiatric clinic and those of contrast cases of girls from mainstream classrooms of one Goteborg school district. To avoid overreliance on the male prototype with regard to diagnostic criteria the clinical group comprised a mixed sample of girls and boys without diagnostic subgrouping. Clinic girls had a lower IQ than comparison girls. Girls were more impaired than the boys with respect to executive functions and scored less well on theory of mind tasks. Previous studies have shown girls with autism and mental retardation to be more severely affected than boys both with regard to level of intellectual functioning and overall measures of brain dysfunction. The present study indicates that clinic girls with a variety of neuropsychiatric disorders at higher levels of intellectual functioning (some of which met diagnostic criteria for autism spectrum disorder) may also be more severely affected than boys with corresponding types of "surface" problems.

3.1.122. Bodfish, J.W., Symons, F.J., Parker, D.E., Lewis, M.H. "Varieties of repetitive behavior in autism: comparisons to mental retardation." *J Autism Dev Disord* 2000 Jun;30(3):237-43.

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Systematic study of abnormal repetitive behaviors in autism has been lacking despite the diagnostic significance of such behavior. The occurrence of specific topographies of repetitive behaviors as well as their severity was assessed in individuals with mental retardation with and without autism. The occurrence of each behavior category, except dyskinesias, was higher in the autism group and autistic subjects exhibited a significantly greater number of topographies of stereotypy and compulsions. Both groups had significant patterns of repetitive behavior co-occurrence. Autistic subjects had significantly greater severity ratings for compulsions, stereotypy, and self-injury. Repetitive behavior severity also predicted severity of autism. Although abnormal repetition is not specific to autism, an elevated pattern of occurrence and severity appears to characterize the disorder.

3.1.123. Rieffe, C., Meerum Terwogt, M., Stockmann, L. "Understanding atypical emotions among children with autism." *J Autism Dev Disord* 2000 Jun;30(3):195-203.

Free University, Amsterdam, The Netherlands.

Children with autism are said to be poor mind readers: They have a limited understanding of the role that mental states play in determining emotions and behavior. In this research,

23 high-functioning children from the autistic spectrum (M age 9 years 3 months), 42 6-year-old controls, and 43 10-year-old controls were presented with six emotion-evoking stories and they were asked to explain protagonists' typical and atypical emotions. In the case of typical emotions, as expected on the basis of the mindblind hypothesis, children from the autistic spectrum gave few mental state explanations, referring to fewer than even the 6-year-old control group. However, in the case of atypical emotions, the autistic group performed as well as the 10-year-old controls. Their explanations for the atypical emotions demonstrate that children from the autistic spectrum indeed have the capacity to mind read (with respect to both desires and beliefs), although they do not always use this capacity in the same way as normally developing children. It is argued that the mind-reading capacity of high-functioning children from the autistic spectrum might be basically intact; unused in everyday circumstances but not necessarily defective.

3.1.124. Luteijn, E., Luteijn, F., Jackson, S., Volkmar, F., Minderaa, R. "The children's Social Behavior Questionnaire for milder variants of PDD problems: evaluation of the psychometric characteristics." *J Autism Dev Disord* 2000 Aug;30(4):317-30.

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The Children's Social Behavior Questionnaire (CSBQ) contains items referring to behavior problems seen in children with milder variants of PDD. Data of large samples of children diagnosed as having high-functioning autism, PDDNOS, ADHD, and other child-psychiatric disorders were gathered. Besides the CSBQ, parents completed the Autism Behavior Checklist (ABC) and the Child Behavior Checklist (CBCL). The data provided the basis for scale construction of the CSBQ, a comparison of the CSBQ scales with other instruments and a comparison of groups on scores on the CSBQ. The 5 scales obtained referred to Acting-out behaviors, Social Contact problems, Social Insight problems, Anxious/Rigid behaviors and Stereotypical behaviors. Results show that the CSBQ has good psychometric qualities with respect to both reliability and validity. A comparison of the different groups showed that significant group differences were found on all scales. In general, the autism group received the highest scores, followed by the PDDNOS group and the ADHD group. Exceptions were on the Acting-out scale, where the ADHD group scored highest and on the Social Insight scale, where no significant difference was found between the PDDNOS group and the ADHD group. Implications of the results and suggestions for further research are discussed.

3.1.125. Rinehart, N.J., Bradshaw, J.L., Moss, S.A., Brereton, A.V., Tonge, B.J. "Atypical interference of local detail on global processing in high-functioning autism and Asperger's disorder." *J Child Psychol Psychiatry* 2000 Sep;41(6):769-78.

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This study explored the claim that individuals with autism and Asperger's disorder tend to process locally rather than holistically. Participants observed a large or "global" number composed of smaller or "local" numbers. The response was contingent upon the identification of either the large stimulus or the small stimuli. Relative to age, sex, and IQ matched controls, global processing in children and adolescents with autism (N = 12) and Asperger's disorder (N = 12) was more vulnerable when the local stimuli were incongruent. The autism group made more global errors than their matched control group, regardless of whether there was local incongruence. In contrast, the Asperger's disorder group made a similar number of global errors as their respective control group. These results were discussed in relation to an "absence of global precedence" notion, "weak central coherence" theory, and right-hemisphere dysfunction. The neurobiological significance of these findings were discussed in the context of a fronto-striatal model of dysfunction.

3.1.126. Rutter, M., Sroufe, L.A. "Developmental psychopathology: concepts and challenges." *Dev Psychopathol* 2000 Summer;12(3):265-96. Publication Types: Review, Review, Tutorial.

University of London, UK.

The defining features of developmental psychopathology concepts include attention to the understanding of causal processes, appreciation of the role of developmental mechanisms, and consideration of continuities and discontinuities between normality and psychopathology. Accomplishments with respect to these issues are reviewed in relation to attachment disorders, antisocial behavior, autism, depressive disorder, schizophrenia, and intellectual development. Major research challenges remain in relation to measurement issues, comorbidity, gender differences, cognitive processing, nature-nurture interplay, heterotypic continuity, continuities between normal variations and disorders, developmental programming, and therapeutic mechanisms in effective treatments.

3.1.127. Ben Shalom, D. "Developmental depersonalization: the prefrontal cortex and self-functions in autism." *Conscious Cogn* 2000 Sep;9(3):457-60. Publication Types: Comment.

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The human self model suggests that the construct of self involves functions such as agency, body-centered spatial perspectivity, and long-term unity. Vogeley, Kurthen, Falkai, and Maieret (1999) suggest that agency is subserved by the prefrontal cortex and other association areas of the cortex, spatial perspectivity by the prefrontal cortex and the parietal lobes, and long-term unity by the prefrontal cortex and the temporal lobes and that all of these functions are impaired in schizophrenia. Exploring the connections between the prefrontal cortex and the construct of self, the present article extends the application of the self model to autism. It suggests

that in contrast to schizophrenia, agency and spatial perspectivity are probably preserved in autism, but that, similarly to schizophrenia, long-term unity is probably impaired. This hypothesis is compatible with a model of neuropsychological dysfunction in autism in a neural network including parts of the prefrontal cortex, the temporal lobes, and the cerebellum. Copyright 2000 Academic Press.

3.1.128. Sandman, C.A., Hetrick, W., Talyor, D., Marion, S., Chicz-DeMet, A. "Uncoupling of proopiomelanocortin (POMC) fragments is related to self-injury." *Peptides* 2000 Jun;21(6):785-91.

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Proopiomelanocortin (POMC) contains several interesting, behaviorally active peptides. Release patterns of these fragments have been related to bizarre episodes of self-injurious behavior (SIB) among autistic individuals. Moreover, elevation in beta-endorphin (betaE) but not ACTH levels was associated with a positive response to an acutely administered, centrally acting opioid blocker among autistic individuals exhibiting SIB. In the present study, POMC fragments were measured in 12 self-injurious patients before and after long term (3 month) treatment with an opiate blocker naltrexone (NTX). POMC fragments were sampled from blood collected at the beginning of the baseline and placebo-controlled treatment phases of the study. Results indicated that the co-release (coupling) of POMC fragments were stable over time and the profile of POMC fragments in plasma predicted the effectiveness of a CNS acting drug in autistic subjects who self-injure.

3.1.129. Miller, J.N., Ozonoff, S. "The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology." *J Abnorm Psychol* 2000 May;109(2):227-38.

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The present study compared individuals with high-functioning autism (HFA) and Asperger disorder (AD) in intellectual, motor, visuospatial, and executive function domains. Participants with AD demonstrated significantly higher Verbal and Full Scale IQ scores, significantly larger Verbal-Performance IQ discrepancies, and significantly better visual-perceptual skills than those with HFA. Once the superior intellectual abilities of the AD group were controlled (both statistically through analysis of covariance and by examining IQ-matched subgroups of HFA and AD participants), no significant group differences in motor, visuospatial, or executive functions were evident, save a marginally significant trend toward poorer fine motor performance in the AD group. This suggests that AD may simply be "high-IQ autism" and that separate names for the disorders may not be warranted. The relation of these findings to theories of autism and AD are discussed.

3.1.130. Bradshaw, J.L., Sheppard, D.M. "The neurodevelopmental frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization." *Brain Lang* 2000 Jun 15;73(2):297-320. Publication Types: Review, Review, Tutorial.

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The frontostriatal system (dorsolateral prefrontal cortex, lateral orbitofrontal cortex, anterior cingulate, supplementary motor area, and associated basal-ganglia structures) is subject to a range of neurodevelopmental disorders: Tourette's syndrome (TS), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), autism, and probably depression. The system is responsible for our adaptive responses (initiation, execution, or withholding) to environmental situations, and the above disorders, involving effectively excessive release or withholding of various types of response, are all a consequence of changes in specific frontostriatal regions. The disorders all have a genetic component, and their persistence in the genome indicates that their clinical manifestations may also be associated, perhaps in low levels in close relatives, with certain adaptive advantages in given situations. Thus autism is associated with computational careers, depression with literary creativity, SCZ with lateral thinking and the Odyssean personality, ADHD with an Ice-Age readiness to respond, OCD with a focused range of interests, and TS with competitive sports and jazz improvisation. The disorders are all highly comorbid, and which one predominantly manifests may depend on how the frontostriatal system happens to be compromised as a result of inherited genetic predispositions and environmental contingency. We review the adaptive nature of the various subclinical manifestations and the evidence for concomitant phenomena (possibly epiphenomena): alterations in structural, functional, and behavioral lateralization in each syndrome. Indeed it is not clear that altered lateralization in frontostriatal disorders of a neurodevelopmental origin generally has any adaptive significance; it may often simply serve as a marker for altered regulatory function of the frontostriatal system, alterations which in low genetic dosage or penetrance continue to play an adaptive role in clinically unaffected close relatives of probands, but which, in high dosage or penetrance in the probands themselves, are generally deleterious. Copyright 2000 Academic Press.

3.1.131. Harris, S.L., Handleman, J.S. "Age and IQ at intake as predictors of placement for young children with autism: a four- to six-year follow-up." *J Autism Dev Disord* 2000 Apr;30(2):137-42.

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The predictive power of age and IQ at time of admission to an intensive treatment program using applied behavior analysis were examined in a 4- to 6-year follow-up of educational placement. Twenty-seven children with autistic disorder who were between the ages of 31 and 65 months and

had IQs on the Stanford Binet between 35 and 109 at time of admission to the Douglass Developmental Disabilities Center were followed up 4 to 6 years after they left the preschool. The results showed that having a higher IQ at intake (M = 78) and being of younger age (M = 42 months) were both predictive of being in a regular education class after discharge, whereas having a lower IQ (M = 46) and being older at intake (M = 54 months) were closely related to placement in a special education classroom. The results are interpreted as pointing to the need for very early intervention for children with Autistic Disorder. It is also emphasized that older children and those with lower IQs in the present study showed measurable gains in IQ from treatment. The data should not be taken to suggest that children older than 4 years of age do not merit high quality treatment.

3.1.132. Davidovitch, M., Glick, L., Holtzman, G., Tirosh, E., Safir, M.P. "Developmental regression in autism: maternal perception." *J Autism Dev Disord* 2000 Apr;30(2):113-9.

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Developmental regression among children with autism is a common phenomenon of unknown origin. The purpose of this study was to identify the differences between children with autism who reportedly regressed with those who did not regress. A representative group of 39 mothers were interviewed (40 children—1 pair of twin girls) about familial, pregnancy, perinatal, as well as medical history and developmental milestones. The study focused on mothers' perceptions of developmental regression. Nineteen children (47.5%) regressed in verbal and nonverbal communication and social but not in motor abilities. Mean age of regression was 24 months, with 11 children who regressed before and 8 after this age. No significant differences were reported by mothers of children who did or did not regress. More mothers of children who regressed, than those of children who did not, expressed guilt feelings regarding the development of autism, and almost all of them had an "explanation" for the possible mechanisms that might have influenced their children's developmental course. In conclusion, developmental regression in our population appears to be a typical event in the natural course of autism. There is little difference between those children who regressed and those who did not regress in maternal perceptions and reports of development, family, and medical history.

3.1.133. Bailey, D.B. Jr, Hatton, D.D., Mesibov, G., Ament, N., Skinner, M. "Early development, temperament, and functional impairment in autism and fragile X syndrome." *J Autism Dev Disord* 2000 Feb;30(1):49-59.

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We compared the developmental status, functional abilities, and temperament of 31 young boys with fragile X syndrome (FXS) who did not have autism, matched on chronological age, gender, and race, with 31 boys with autism but no FXS. Children with autism exhibited a more variable profile of

development in comparison with a relatively flat profile for children with FXS. Children with autism were significantly more delayed in social skills and were rated by observers as exhibiting a greater degree of impairment in cognitive, communication, and social skills. On temperament ratings, both groups were slower to adapt, less persistent, and more withdrawing than the reference group. Boys with FXS were rated as more active than the referent group, whereas boys with autism were rated as less intense, more distractible, having a higher threshold for response, and less rhythmic than the reference group. A smaller three-group analysis compared boys with FXS, boys with autism, and boys with both FXS and autism. Children with both autism and FXS were substantially more delayed than children with autism or FXS alone.

3.1.134. Millward, C., Powell, S., Messer, D., Jordan, R. "Recall for self and other in autism: children's memory for events experienced by themselves and their peers." *J Autism Dev Disord* 2000 Feb;30(1):15-28.

Division of Education, University of Hertfordshire, Watford, United Kingdom.

Research on memory processing suggests that memory for events that an individual experiences should be superior to that for similar events that someone else experiences (e.g., Baker-Ward et al., 1990). However, such predictions may not be applicable to individuals with autism. There are already suggestions that individuals with autism have specific difficulties in remembering (Boucher & Lewis, 1989). In addition, they are known to have more general difficulties involving processes related to the "self." If children with autism have difficulties in encoding information about themselves this could result in a deficit in personal episodic memory. The studies reported here compare memory for personally experienced events with that of memory for events experienced by a peer. An adaptation of a method devised by Boucher and Lewis has been employed to assess recall. Two separate studies were conducted to investigate whether children with autism are impaired at recalling personal events. Two groups of children took part in Study 1, a group of children with autism and a control group of typical children matched for verbal mental age. A group of children with moderate learning difficulties were employed in the second study to investigate whether the findings also occur in other groups of individuals who have learning disabilities. Findings indicate that, in the group with autism, events performed by the individual were recalled significantly less well than the observed events performed by a peer. However, the results for the nonautistic children in both studies showed that the opposite was true. Theoretical claims are discussed in the light of these findings.

3.1.135. Renner, P., Klinger, L.G., Klinger, M.R. "Implicit and explicit memory in autism: is autism an amnesic disorder?" *J Autism Dev Disord* 2000 Feb;30(1):3-14.

Department of Psychology, University of Alabama, Tuscaloosa 35487, USA.

Medial temporal lobe amnesic disorder is characterized by an impairment in explicit memory (e.g., remembering a shopping list) and intact implicit memory (e.g., a woman seems familiar although you cannot remember having met her before). This study examined whether children with high-functioning autism have this same dissociation between explicit and implicit memory abilities. Children with autism and normal development participated in three memory tasks: one implicit task (perceptual identification) and two explicit tasks (recognition and recall). Children with autism showed intact implicit and explicit memory abilities. However, they did not show the typical pattern of recalling more items from both the beginning and end of a list and instead only recalled items from the end of the list. These results do not support the theory that high-functioning autism is a type of medial temporal lobe amnesia. However, these findings suggest that persons with autism use different organizational strategies during encoding or retrieval of items from memory.

3.1.136. Leevers, H.J., Harris, P.L. "Counterfactual syllogistic reasoning in normal 4-year-olds, children with learning disabilities, and children with autism." *J Exp Child Psychol* 2000 May;76(1):64-87.

Center for Molecular and Behavioral Neuroscience, Aidekman Research Center, Rutgers University, Newark, NJ 07102, USA. leevers@axon.rutgers.edu

Instruction encouraging imagery improves logical reasoning with counterfactual premises by normal preschool children. In contrast, children with autism have been reported to reason accurately with counterfactual premises in the absence of such instruction (F. J. Scott, S. Baron-Cohen, & A. M. Leslie, 1999). To investigate this pattern of findings, we compared the performance of children with autism, children with learning disabilities, and normally developing 4-year-olds, who were given reasoning problems both with and without instruction in two separate testing sessions 2 to 3 weeks apart. Overall, instruction to use imagery led to persistent logical performance. However, children with autism displayed a distinctive pattern of responding, performing around chance levels, showing a simple response bias, and rarely justifying their responses by elaborating on the premises. We propose that instruction boosts logical performance by clarifying the experimenter's intention that a false proposition be accepted as a basis for reasoning and that children with autism have difficulty grasping this intention. Copyright 2000 Academic Press.

3.1.137. McCabe, K.A., Smith, V.L., LePore, M. "Intentionality detection and "mindreading": why does game form matter?" *Proc Natl Acad Sci U S A* 2000 Apr 11;97(8):4404-9.

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By around the age of 4 years, children "can work out what people might know, think or believe" based on what they say or do. This is called "mindreading," which builds upon the human ability to infer the intentions of others. Game theory makes a strong assumption about what individual A can

expect about B's intentions and vice versa, viz. that each is a self-interested opponent of the other and will reliably analyze games by using such basic principles as dominance and backward induction, and behave as if the normal form of an extensive form game is equivalent to the latter. But the extensive form allows intentions to be detected from actual sequential play and is therefore not necessarily equivalent psychologically to the normal form. We discuss Baron-Cohen's theory of the mindreading system [Baron-Cohen, S. (1995) *Mindblindness: An Essay on Autism and Theory of Mind* (MIT Press, Cambridge, MA)] to motivate the comparison of behavior in an extensive form game with its corresponding normal form. As in the work of Rapoport [Rapoport, A. (1997) *Int. J. Game Theory* 26, 113-136] and Schotter et al. [Schotter, A., Wiegelt, K. & Wilson, C. (1994) *Games Econ. Behav.* 6, 445-468], we find consistent differences in behavior between the normal and extensive forms. In particular, we observe attempts to cooperate, and in some treatments we observe the achievement of cooperation, occurring more frequently in the extensive form. Cooperation in this context requires reciprocity, which is more difficult to achieve by means of intentionality detection in the normal as opposed to the extensive form games we study.

3.1.138. Leekam, S.R., Lopez, B., Moore, C. "Attention and joint attention in preschool children with autism." *Dev Psychol* 2000 Mar;36(2):261-73.

Department of Psychology, University of Kent at Canterbury, England. S.R.Leekam@durham.ac.uk

Three experiments examined the role of attention in explaining dyadic (child-adult) and triadic (child-adult-object) joint attention difficulties in autism. Experiments 1 and 2 investigated children's ability to orient to an adult's attention bid and to follow the direction of a human or nonhuman cue. Experiment 3 tested ability to disengage and shift attention to objects. Results showed autism-specific difficulties at both dyadic and triadic levels. Children with autism were less responsive than developmentally delayed controls in orienting to attention bids and in following a human head-turn cue yet had no difficulty in shifting attention and were faster overall in orienting to targets. Results suggest a specific developmental delay in which children with autism rely on the presence of objects in the visual field to guide action. The relation between this problem and autistic children's difficulties with human communicative signals is discussed.

3.1.139. Elia, M., Ferri, R., Musumeci, S.A., Del Gracco, S., Bottitta, M., Scuderi, C., Miano, G., Panerai, S., Bertrand, T., Grubar, J.C. "Sleep in subjects with autistic disorder: a neurophysiological and psychological study." *Brain Dev* 2000 Mar;22(2):88-92.

Department of Neurology, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Via Conte Ruggero 73, 94018, Troina, Italy. melia@oasi.en.it

Polysomnography (EOG, EEG, EMG) was carried out in 17 male children and adolescents with autistic disorder, in seven patients with mental retardation and fragile X syndrome, and in five age- and sex-matched normal male subjects. Density

of rapid eye movements was not significantly different in the three groups of subjects; however, some sleep parameters such as time in bed, sleep period time, and total sleep time were significantly lower in subjects with autistic disorder than in normal controls; moreover, patients with autistic disorder showed values of sleep period time, first REM latency and percent (%) sleep stage 1 lower than those of patients with fragile X syndrome with mental retardation. Density of muscle twitches was significantly higher in patients with autistic disorder than in normal controls. In contrast only minor differences were observed between patients with autistic disorder and those with fragile X syndrome with mental retardation. Furthermore, some psychoeducational profile-revised items such as perception and eye-hand coordination, showed significant correlation with some sleep parameters (time in bed, sleep latency, stage shifts, first REM latency and wakefulness after sleep onset). Childhood Autism Rating Scale (CARS) scores to visual response and non-verbal communication showed significant correlation with some tonic sleep parameters, such as sleep period time, wakefulness after sleep onset, and total sleep time. Relating to people and activity level items were found to be significantly correlated with rapid eye movement density. Our results suggest the existence of a sleep pattern in autistic patients different from that observed in subjects with mental retardation and from that of normal controls. In addition, these findings indicate that sleep parameters in these patients are correlated with some psychological indices generally used for the diagnosis of autistic disorder; for this reason, polysomnographies might be useful in the comprehension of the neurophysiological mechanisms underlying this condition.

3.1.140. Verri, A., Uggetti, C., Vallero, E., Ceroni, M., Federico, A. "Oral self-mutilation in a patient with rhombencephalosynapsis." *J Intellect Disabil Res* 2000 Feb;44 (Pt 1):86-90. Publication Types: Review, Review of Reported Cases.

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Rhombencephalosynapsis (RS) is a rare cerebellar malformation. Its essential features are the absence of the incisura cerebelli posterior, fusion of the cerebellar hemispheres, the absence of the velum medullare anterius and nuclei fastigii, and fusion of the dentate nuclei, which are shifted towards the mid-line. Clinically, affected patients present with signs of cerebellar and motor disturbances. The present report describes a new patient affected by RS. The subject first presented at the age of 22 years because of a psychiatric symptomatology which was characterized by obsessive oral self-mutilation associated with an intellectual disability. Objective evaluation documented dysmorphic features, while neurological examination showed only a slight truncal ataxia. The subject's IQ was 74 on the Wechsler Scale (verbal IQ = 79, performance IQ = 74). Psychiatric evaluation with DSM-IV criteria documented an obsessive-compulsive personality disorder associated with emotional instability and oral self-mutilation. The typical picture of rhombencephalosynapsis was evident on magnetic resonance

imaging. Both chromosomal analysis and routine biochemical investigations were normal. The relationship between oral self-injurious behaviour and cerebellar malformations is discussed with particular regard to the behavioural aspects of cerebellar congenital pathology in affective disorders and in autism.

3.1.141. Jarrold, C., Butler, D.W., Cottington, E.M., Jimenez, F. "Linking theory of mind and central coherence bias in autism and in the general population." *Dev Psychol* 2000 Jan;36(1):126-38.

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Three experiments investigated whether 2 characteristic aspects of the psychological profile of autism, theory-of-mind deficits and weak central coherence, might be functionally related. Experiment 1 showed that in the general population, performance on a proposed test of theory of mind was inversely related to speed on the Embedded Figures Test, a measure of central coherence bias. Experiments 2 and 3 confirmed that poor theory-of-mind performance was linked to weak central coherence among typically developing children and among children with autism; however, the correlations between these measures were reliable only after accounting for differences in individuals' verbal mental ages. This pattern of results is interpreted in terms of a relationship between individual differences in theory of mind and central coherence bias, a relationship that is separate from any developmental differences in these domains.

3.1.142. Scourfield, J., Martin, N., Lewis, G., McGuffin, P. "Heritability of social cognitive skills in children and adolescents." *Br J Psychiatry* 1999 Dec;175:559-64. Publication Types: Twin Study.

Department of Psychological Medicine, University of Wales College of Medicine, Cardiff.

BACKGROUND: Social cognitive skills are those which enable understanding of social situations; they are relevant to a variety of psychiatric disorders including autism, schizophrenia and externalizing behaviour problems in children. AIMS: To examine the heritability of social cognitive skills. METHOD: Using a population-based sample of twins aged 5-17, the genetic and environmental influences on social cognitive skills were examined. RESULTS: Male scores were higher than female scores ($P < 0.001$), indicating poorer social cognition among males. A heritability of 0.68 (95% CI 0.43-0.78) was found, with shared environmental influences accounting for only 0.05 of the variance (95% CI 0.00-0.28). This could be removed from the model without worsening the fit. There were no significant differences in genetic effects between the genders, but age-related changes were found, with younger twins showing greater genetic influence on social cognition. CONCLUSIONS: Social cognition appears to be under considerable genetic influence in the population and shows significant male-female differences. No gender differences in genetic influences on the variance of scores were found, but the effects of age were significant.

3.1.143. Baron-Cohen, S., Wheelwright, S. **"'Obsessions' in children with autism or Asperger syndrome. Content analysis in terms of core domains of cognition."** *Br J Psychiatry* 1999 Nov;175:484-90.

Department of Experimental Psychology, University of Cambridge.

BACKGROUND: We report a survey of the content of obsessions in children with autism spectrum conditions. We use the term 'obsessions' narrowly, to indicate strong, repetitive interests. We predicted that obsessions would not cluster randomly, but rather would occur significantly more often in the domain of 'folk physics' (an interest in how things work), and significantly less often in the domain of 'folk psychology' (an interest in how people work). These predictions were tested relative to a control group of 33 children with Tourette syndrome. **AIMS:** To examine the content of autistic obsessions, and to test the theory that these reflect an evolved cognitive style of good folk physics alongside impaired folk psychology. **METHOD:** Ninety-two parents returned a questionnaire designed to determine the subject of their child's obsessional interests. The results were analysed in terms of core domains of cognition. **RESULTS:** Both predictions were confirmed. **CONCLUSIONS:** These results suggest that impaired folk psychology and superior folk physics are part of the cognitive phenotype of autism. A content-free theory of obsessions is inadequate.

3.1.144. Bernabei, P., Palli, F.G., Levi, G., Mazzoncini, B., Cannoni, E. **"Disturbance of imagination and symbolization in pervasive developmental disorders: preliminary study utilizing the Rorschach Inkblot Test."** *Percept Mot Skills* 1999 Dec;89(3 Pt 1):917-30.

Department of Childhood Neurological and Psychiatric Sciences, University of Rome La Sapienza, Italy. pbernabei@axrma.uniroma1.it

Two clinical cases of children of 6 and 7 years are presented with their respective Rorschach records. The first case had a diagnosis of autism, the second of Pervasive Developmental Disorder Not Otherwise Specified. The modes of elaboration and responses to the ambiguous stimuli of the Rorschach test were compared with the clinical symptoms of the two subjects, which are centered on the two opposite poles of absence of imagination in the first case and distortion of the imaginative processes in the second.

3.1.145. Serra, M., Minderaa, R.B., van Geert, P.L., Jackson, A.E. **"Social-cognitive abilities in children with lesser variants of autism: skill deficits or failure to apply skills?"** *Eur Child Adolesc Psychiatry* 1999 Dec;8(4):301-11.

University Centre for Child and Adolescent Psychiatry, Groningen, The Netherlands.

The present study re-examined the ability of children with lesser variants of autism (classified as PDD-NOS) to infer emotions of other people and to describe others in terms of inner, psychological characteristics. It also explores the

hypothesis that these children may have the skill to infer mental states of other people, but fail to use these skills spontaneously. Children with lesser variants of autism and normal control children matched for age, sex and intelligence were given three structured emotional role-taking tasks and asked to give two spontaneous descriptions of peers. The results showed that both groups did not differ with respect to their ability to infer other people's emotions in the structured role-taking tasks. In contrast, significant differences were found on the free person descriptions: the children with PDD-NOS used fewer inner, psychological characteristics to describe peers.

3.1.146. Gorman, B.J. **"Facilitated communication: rejected in science, accepted in court—a case study and analysis of the use of FC evidence under Frye and Daubert."** *Behav Sci Law* 1999;17(4):517-41. Publication Types: Review, Review, Tutorial.

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This article traces the phenomenon of facilitated communication (FC) from its introduction to the United States in 1990 to its use in recent court proceedings. FC is an alleged breakthrough technique that enables nonverbal individuals with developmental disabilities to communicate via a form of assisted typing. Widespread use of FC resulted in miraculous communications and surprising allegations of abuse. The growing importance and notoriety of FC attracted the interest of the scientific community which rejected the technique after numerous controlled studies were undertaken. Despite the rejection of FC by the scientific community, however, some courts have accepted this unproven technique by evading their state's test of scientific admissibility. It is asserted that court decisions admitting FC evidence are pretextual, and it is argued that FC should not be admitted into court proceedings. In addition, this report analyzes the future of FC in those states that have adopted the newer Daubert standard for scientific evidence. Copyright 1999 John Wiley & Sons, Ltd.

3.1.147. Adelinis, J.D., Hagopian, L.P. **"The use of symmetrical 'do' and 'don't' requests to interrupt ongoing activities."** *J Appl Behav Anal* 1999 Winter;32(4):519-23.

Kennedy Krieger Institute and The Johns Hopkins University School of Medicine, USA.

The results of a modified functional analysis demonstrated that aggression, displayed by a 27-year-old man, was occasioned by the use of "don't" requests to interrupt the client's ongoing and often inappropriate activities (e.g., lying on the floor, pica, inappropriate touching of others). Subsequent analyses demonstrated that aggression was lower when ongoing activities were interrupted with symmetrical "do" requests than with "don't" requests. An intervention utilizing symmetrical "do" requests (i.e., prompting an individual to engage in an incompatible behavior) to interrupt such activities resulted in reduced levels of aggression.

3.1.148. Vollmer, T.R., Borrero, J.C., Lalli, J.S., Daniel, D. "Evaluating self-control and impulsivity in children with severe behavior disorders." *J Appl Behav Anal* 1999 Winter;32(4):451-66.

Psychology Department, University of Florida, Gainesville 32611, USA.

Impulsivity and self-control involve a choice between a smaller, more immediate reinforcer and a larger, more delayed reinforcer. Impulsive behavior occurs when responding produces the more immediate, relatively smaller reinforcers at the expense of delayed larger reinforcers. Self-control occurs when responding produces delayed larger reinforcers at the expense of immediate smaller reinforcers. Recently, researchers in applied behavior analysis have suggested that evaluations of self-control and impulsivity are relevant to socially important behaviors. Further, common behavioral treatments such as differential reinforcement may be influenced by variables such as reinforcer delay. In this study, we showed that aggression, reinforced by access to food, could be maintained as impulsive behavior. The participants were 2 young boys with severe developmental disabilities. For both participants, descriptive observations, care provider report, and functional analyses suggested that aggression was reinforced by food access (and television access for 1 participant). Next, we introduced a differential reinforcement procedure in which appropriate mands were reinforced. After various manipulations, we showed that aggression occurred when it produced immediate but small reinforcers even though mands produced larger, more delayed reinforcers. However, both participants displayed self-control when the delay to reinforcement was signaled (with a hand gesture or a timer).

3.1.149. Klin, A., Sparrow, S.S., de Bildt, A., Cicchetti, D.V., Cohen, D.J., Volkmar, F.R. "A normed study of face recognition in autism and related disorders." *J Autism Dev Disord* 1999 Dec;29(6):499-508.

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Although the interpretation of studies of face recognition in older children, adolescents, and adults with autism is complicated by the fact that participating samples and adopted methodologies vary significantly, there is nevertheless strong evidence indicating processing peculiarities even when task performance is not deficient. Much less is known about face recognition abilities in younger children with autism. This study employed a well-normed task of face recognition to measure this ability in 102 young children with autism, pervasive developmental disorder not otherwise specified (PDDNOS), and non-PDD disorders (mental retardation and language disorders) matched on chronological age and nonverbal mental age, and in a subsample of 51 children divided equally in the same three groups matched on chronological age and verbal mental age. There were pronounced deficits of face recognition in the autistic group relative to the other nonverbally matched and verbally matched groups. Performance on two comparison

tasks did not reveal significant differences when verbal ability was adequately controlled. We concluded that young children with autism have face recognition deficits that cannot be attributed to overall cognitive abilities or task demands. In contrast to controls, there was a lower correlation between performance on face recognition and nonverbal intelligence, suggesting that in autism face recognition is less correlated with general cognitive capacity. Contrary to our expectation, children with PDDNOS did not show face recognition deficits.

3.1.150. Garner, C., Callias, M., Turk, J. "Executive function and theory of mind performance of boys with fragile-X syndrome." *J Intellect Disabil Res* 1999 Dec;43 (Pt 6):466-74.

Children's Department, South London and Maudsley NHS Trust, Maudsley Hospital, UK.

Fragile-X syndrome is the most common genetically inherited cause of intellectual disability. People with this syndrome typically show a behavioural profile of abnormal social interactions which are similar in some ways to those seen in people with autism. The present study investigated whether cognitive processes which have been hypothesized to underlie social abnormalities associated with autism are also impaired in boys with fragile-X syndrome without autistic spectrum disorders. Eight boys with fragile-X syndrome and eight with intellectual disability of unknown aetiology, matched on receptive verbal ability, age and with no diagnosis of autism, were tested on a battery of theory of mind and executive function tasks. Significantly more boys with fragile-X syndrome failed the simplest theory of mind task. However, this could be attributed to overall level of ability rather than group membership. No differences were found between the groups on any other measures used. A proportion of both groups failed first- and second-order false belief tasks. The performance of both groups on the executive function measure was at the floor of the test. At low levels of overall ability, the performance of boys with fragile-X syndrome and boys with intellectual disability of unknown aetiology may be more similar than they are different. The implication of this result for clinical interventions is discussed.

3.1.151. Ropar, D., Mitchell, P. "Are individuals with autism and Asperger's syndrome susceptible to visual illusions?" *J Child Psychol Psychiatry* 1999 Nov;40(8):1283-93

School of Psychology, University of Nottingham, University Park, UK.

A recent finding that individuals with autism are not susceptible to illusions has been explained by Happe (1996) as a sign of "weak central coherence" at lower levels of processing. We investigated the phenomenon with a more sophisticated measure. In Experiment 1, individuals with autism, Asperger's syndrome, moderate learning difficulties, and typical development adjusted certain comparison lines and circles to make them appear to be the same size in four visual illusions. With a minor exception, the participants with autism and Asperger's syndrome evinced a systematic bias in their judgements in the illusion condition. The extent of this was no different from control participants. In a second

experiment, a similar finding was obtained in a task where participants made verbal judgements about the stimuli. The results suggest that lower-level coherence in visual processing in autism is intact.

3.1.152. Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., Plaisted, K. "Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism." *J Autism Dev Disord* 1999 Oct;29(5):407-18.

Department of Experimental Psychology, University of Cambridge, United Kingdom.

Most theory of mind (ToM) tests are designed for subjects with a mental age of 4-6 years. There are very few ToM tests for subjects who are older or more able than this. We report a new test of ToM, designed for children 7-11 years old. The task involves recognizing faux pas. Study 1 tested 7-9, and 11-year-old normal children. Results showed that the ability to detect faux pas developed with age and that there was a differential developmental profile between the two sexes (female superiority). Study 2 tested children with Asperger syndrome (AS) or high-functioning autism (HFA), selected for being able to pass traditional 4- to 6-year level (first- and second-order) false belief tests. Results showed that whereas normal 9- to 11-year-old children were skilled at detecting faux pas, children with AS or HFA were impaired on this task. Study 3 reports a refinement in the test, employing control stimuli. This replicated the results from Study 2. Some patients with AS or HFA were able to recognize faux pas but still produced them. Future research should assess faux pas production.

3.1.153. Jolliffe, T., Baron-Cohen, S. "The Strange Stories Test: a replication with high-functioning adults with autism or Asperger syndrome." *J Autism Dev Disord* 1999 Oct;29(5):395-406.

Department of Experimental Psychology, University of Cambridge, United Kingdom.

Two groups of individuals, one with high-functioning autism and the other with Asperger syndrome were tested using Happe's Strange Stories Test of a more advanced theory of mind (Happe, 1994). This assesses the ability to interpret a nonliteral statement. Relative to normal controls who were IQ and age-matched, individuals with autism or Asperger syndrome performed less well on the task, while performing normally on a non-mentalistic control task. Individuals with autism or Asperger syndrome could provide mental state answers, but had difficulty in providing contextually appropriate mental state answers. Rather, their answers tended to concentrate on the utterance in isolation. This replicates Happe's result. Although the majority of both clinical groups provided context-inappropriate interpretations, the autism group had the greater difficulty. Results are discussed in relation to both weak central coherence and theory of mind.

3.1.154. Williams, E., Costall, A., Reddy, V. "Children with autism experience problems with both objects and people." *J Autism Dev Disord* 1999 Oct;29(5):367-78. Publication Types: Review, Review, Tutorial.

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Kanner (1943), in his classic account, described autism as a specific impairment in interpersonal relations which leaves the child's uses of objects relatively unaffected. This combination of the difficulties in relating to people and the supposedly "excellent" relations to objects figures centrally within many of the current theories of autism, which have had relatively little to say on the question of object use. This paper draws attention to evidence of widespread impairments in relating to objects, not only in interpersonal aspects of object use but also in early sensorimotor exploration and the functional and conventional uses of objects. In stressing these problems with objects, our purpose is not to downplay the social dimension of autism, but rather to highlight the reciprocal nature of the interactions between the child, other people, and objects. Given the evidence that other people play an important role in introducing objects to children, we propose that an impairment in interpersonal relations should itself lead us to expect corresponding disruption in the autistic child's use of objects. Conversely, an unusual use of objects is likely to manifest itself in disturbances in relating to other people, given the importance of a shared understanding and use of objects in facilitating interaction.

3.1.155. Rapin, I., Steinberg, M., Waterhouse, L. "Consistency in the ratings of behaviors of communicatively impaired autistic and non-autistic preschool children." *Eur Child Adolesc Psychiatry* 1999 Sep;8(3):214-24.

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Typically, children with disabilities are evaluated clinically by a number of professionals with different backgrounds whose task is to provide a diagnosis and an intervention plan. This study was carried out to describe interrater agreement for pairs of independent observers rating with different instruments the behaviors of 505 communicatively impaired autistic and nonautistic preschool children. Observers were parents, teachers, neurologists, and psychiatrists. Parents and teachers responded to behavioral questionnaires, neurologists filled out the mental status part of a standardized neurologic evaluation, and psychiatrists an observational questionnaire. All four types of observers rated sociability, language, play, attention, stereotyped, and other aberrant behaviors. Agreement between pairs of raters was significant but moderate. Owing to range restriction with smaller numbers of subjects, agreement decreased for ratings of subsamples divided according to diagnosis, cognitive level, or age. There were some differences among observers' ratings of the severity of particular categories of behaviors, with physicians generally viewing the children as more severely impaired and teachers as least impaired. Interrater agreement was not enhanced

when parents and teachers rated similarly worded behavioral items. Modest interrater agreement in this study, like agreement among disparate raters of children's behaviors in other studies, suggests that observers are sensitive to different aspects of behavior and that their ratings are more likely to be complementary than unreliable.

3.1.156. Gillberg, C. "Neurodevelopmental processes and psychological functioning in autism." *Dev Psychopathol* 1999 Summer;11(3):567-87. Publication Types: Review, Review, Academic.

Department of Child and Adolescent Psychiatry, Annedals Clinics, Goteborg University, Sweden.

Autism is a developmental disorder with variable severity, occurring at all levels of cognitive ability and having a number of slightly different clinical presentations. It is associated with neuropsychological deficits that occur in other conditions also, but its pattern may be specific to autism. Genetic and environmental early insults to brain development are etiological determinants of the disorder. Brain circuitries important for social, communicative, and integrational purposes have been suggested to be dysfunctional in autism. There could be at least two different pathways to autism, one connected with primary temporofrontal dysfunction (and late prenatal-early postnatal origins) and another linked to primary brain-stem dysfunction (and early prenatal origins). Further study of neurodevelopmental and neuropsychological processes in autism will help elucidate not only the pathological mechanisms involved in the specific syndromes but also the underpinnings of normal brain development.

3.1.157. Mouridsen, S.E., Rich, B., Isager, T. "The natural history of somatic morbidity in disintegrative psychosis and infantile autism: a validation study." *Brain Dev* 1999 Oct;21(7):447-52.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

In order to study the validity of disintegrative psychosis (DP) as defined in ICD-9, we compared the natural history of somatic morbidity of 13 patients given this diagnosis in childhood with a control group of 39 patients with infantile autism (IA) matched for gender, age, IQ and social class. Average follow-up time was 22 and 23 (11-33) years, respectively. Significantly more DP patients (85 versus 41%) had been admitted to a non-psychiatric hospital during the follow-up period. They also had significantly more admissions (3.6 versus 1.0) and stayed longer in hospital (78 versus 4 days) than patients with IA. Three of the DP individuals had an associated medical disorder and made extensive use of somatic services during the follow-up period. Altogether the DP group had utilised the medical health care system more than patients with IA suggesting that they had more medical symptoms than the IA group. On the whole our findings suggest that individuals with DP and IA should be conceptualised as essentially distinct and should be studied separately as regards aetiology, pathophysiology, course and treatment.

3.1.158. Ozonoff, S., Williams, B.J., Gale, S., Miller, J.N. "Autism and autistic behavior in Joubert syndrome." *J Child Neurol* 1999 Oct;14(10):636-41.

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To determine whether individuals with Joubert syndrome exhibit features of autism as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), we examined 11 children with Joubert syndrome using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic. Three children met DSM-IV criteria for autistic disorder and one for pervasive developmental disorder not otherwise specified. The other seven all demonstrated at least one DSM-IV symptom of autism, but did not meet criteria for a pervasive developmental disorder. Both total number of DSM-IV symptoms and number of social symptoms distinguished the autism and nonautism subgroups. In contrast, the two subgroups displayed similar levels of communication impairments and repetitive or stereotyped behavior. The key to diagnosing autism in Joubert syndrome is to focus on social behaviors, particularly milestones typically achieved very early in life (eg, attending to human voices, showing objects of interest, enjoyment of social interactions). Implications for the role of the cerebellum in nonmotor behavior and for clinical management of Joubert syndrome also are discussed.

3.1.159. Craig, J., Baron-Cohen, S. "Creativity and imagination in autism and Asperger syndrome." *J Autism Dev Disord* 1999 Aug;29(4):319-26.

Department of Experimental Psychology, University of Cambridge, United Kingdom.

Three studies are reported that address the often described impoverished creativity in autism. Using the Torrance Creativity Tests, Experiment 1 found that children with autism and Asperger syndrome (AS) showed impairments. Experiment 2 tested two explanations of these results: the executive dysfunction and the imagination deficit hypotheses. Results supported both hypotheses. Children with autism and AS could generate possible novel changes to an object, though they generated fewer of these relative to controls. Furthermore, these were all reality-based, rather than imaginative. Experiment 3 extended this using a test of imaginative fluency. Children with autism and AS generated fewer suggestions involving attribution of animacy to foam shapes, compared to controls, instead generating reality-based suggestions of what the shapes could be. Although this is evidence of executive dysfunction, it does not directly account for why imaginative creativity is more difficult than reality-based creativity.

3.1.160. Griffith, E.M., Pennington, B.F., Wehner, E.A., Rogers, S.J. "Executive functions in young children with autism." *Child Dev* 1999 Jul-Aug;70(4):817-32.

Department of Psychology, University of Denver, CO 80208, USA. egriffit@nova.psy.du.edu

The executive dysfunction hypothesis of autism has received support from most studies of older people with autism; however, studies of young children have produced mixed results. Two studies are presented that compare the performance of preschoolers with autism (mean = 51 months/4.3 years of age) to a control group matched on age, and verbal and nonverbal ability. The first study (n = 18 autism and 17 control) found no group differences in performance on 8 executive function tasks (A not B, Object Retrieval, A not B with Invisible Displacement, 3-Boxes Stationary and Scrambled, 6-Boxes Stationary and Scrambled, and Spatial Reversal), but did find that children with autism initiated fewer joint attention and social interaction behaviors. The second (longitudinal) study of a subset of the children (n = 13 autism and 11 control) from the first study found that neither groups' performance on Spatial Reversal changed significantly over the course of a year. The results of these studies pose a serious challenge to the executive dysfunction hypothesis of autism.

3.1.161. Jolliffe, T., Baron-Cohen, S. "A test of central coherence theory: linguistic processing in high-functioning adults with autism or Asperger syndrome: is local coherence impaired?" *Cognition* 1999 Jun 22;71(2):149-85.

Department of Experimental Psychology, University of Cambridge, UK. sb205@cus.cam.ac.uk

Central coherence theory (Frith, U., 1989. *Autism: Explaining the Enigma*. Blackwell, Oxford.) is addressed by exploring linguistic processing in normally intelligent adults with either autism or Asperger syndrome, to test whether local coherence is impaired. Local coherence is the ability to make contextually meaningful connections between linguistic information in short-term or working memory. Experiment 1 demonstrated that individuals with an autism spectrum condition were less likely to use the sentence context spontaneously to provide the context-appropriate pronunciation of a homograph. Experiment 2 presented scenarios which had a situation and outcome which only cohered if a bridging inference was drawn. The clinical groups were less likely to select the most coherent (bridging) inference from competing alternatives. Experiment 3 demonstrated that individuals with an autism spectrum condition were less able to use context to interpret an auditorily presented ambiguous sentence. The findings from Experiments 2 and 3 suggest that individuals with autism or Asperger syndrome have a difficulty in achieving local coherence, while the evidence from Experiment 1 suggests a preference not to strive for coherence. Taken together, these results suggest that individuals with an autism spectrum condition are impaired in achieving local coherence, and they have a preference not to strive for coherence unless instructed to do so, or unless they make a conscious decision to do so. Moreover, the three experiments correlate with one another, which suggests that central coherence may be a unitary force in these different tasks. Of the two clinical groups, the autism group had the greater difficulty in achieving coherence. Possible explanations for the clinical groups' difficulty are explored.

3.1.162. Sicotte, C., Stemberger, R.M. "Do children with PDDNOS have a theory of mind?" *J Autism Dev Disord* 1999 Jun;29(3):225-33.

Loyola College, Baltimore, Maryland, USA.

This study sought to differentiate PDDNOS from a similar nonautistic disorder (i.e., language impairment) on the basis of a cognitive deficit, theory-of-mind (ToM). ToM is an ability to infer mental states in others and has been found to be highly prevalent in autism, a disorder that shares many characteristics with PDDNOS (Baron-Cohen, 1985; Volkmar & Cohen, 1988). A sample of 28 children with either PDDNOS or a language impairment formed two groups (n = 14), matched on gender and verbal mental age. Participants were administered the brain function task (Baron-Cohen, 1989) and the false belief task (Perner, Frith, Leslie, & Leekam, 1989) to assess ToM. Results suggest that children with PDDNOS are deficient in a ToM ability, however, this relationship is not as strong as in previous studies with autistic samples, suggesting that children with PDDNOS may have a greater ToM ability. The existence of PDDNOS on the higher end of a spectrum of the Pervasive Developmental disorders as well as the construct of ToM itself existing on a continuum are discussed.

3.1.163. Volden, J., Johnston, J. "Cognitive scripts in autistic children and adolescents." *J Autism Dev Disord* 1999 Jun;29(3):203-11.

University of Alberta, Edmonton, Canada.

People normally rely on cognitive scripts to structure social interaction. As the dysfunctional social behavior of people with autism extends to situations that are commonly scripted, one wonders whether a partial explanation might be either absent or deficient scriptal representations. Twenty-four relatively high-functioning subjects with autism were compared to typically developing children who had been selected to be similar to the autistic subjects in terms of nonverbal mental age and language level. All subjects were presented with a series of three tasks designed to assess the presence of cognitive social scripts. Results indicated that basic scriptal knowledge was intact but that reliable differences in expressive language persisted.

3.1.164. Potgieter, S.T., Fryns, J.P. "The neurobiology of autism." *Genet Couns* 1999;10(2):117-22. Publication Types: Editorial, Review, Review, Tutorial.

Although the primary cause of autism has not yet been unravelled, a number of genetic conditions have been strongly associated with the behavioural triad of autism. We briefly review the underlying neuropathological, biological and genetic evidence of the possible mechanisms involved in autism. This knowledge should guide accurate investigation of the autistic individual and genetic counselling of parents and family members.

3.1.165. Hering, E., Epstein, R., Elroy, S., Iancu, D.R., Zelnik, N. "Sleep patterns in autistic children." *J Autism Dev Disord* 1999 Apr;29(2):143-7. Publication Types: Clinical Trial, Randomized Controlled Trial.

Department of Pediatrics, Carmel Medical Center, Haifa, Israel.

Sleep disturbances are regarded as a common clinical feature in autistic children. This concept is based primarily on informal observations or studies conducted with questionnaires. In this study we compared data obtained by questionnaires to that obtained with actigraphy. Among 22 autistic children, 12 were reported as having sleep problems and 8 patients completed 72 hours actigraphy. While the employment of questionnaires disclosed that autistic children had an earlier morning awakening time and multiple and early night arousals, actigraphic monitoring showed that with the exception of an earlier morning arousal time ($p = .045$), sleep patterns of autistic children were similar to that of normal children. Parental oversensitivity to sleep disturbances of the autistic children may explain this phenomenon.

3.1.166. Russell, J., Jarrold, C., Hood, B. "Two intact executive capacities in children with autism: implications for the core executive dysfunctions in the disorder." *J Autism Dev Disord* 1999 Apr;29(2):103-12. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Experimental Psychology, Cambridge University, United Kingdom.

Many studies have shown that children with autism perform at a much lower level than control subjects on tests of executive functioning, defined as tasks requiring subjects to hold information in mind while suppressing a prepotent response. These tasks have invariably required subjects to (a) follow arbitrary and novel rules and (b) make a nonverbal response. We report that when one of these features is absent, children with autism are not impaired relative to controls. They perform at a similar level to normally developing children on the "tubes" task (containing no arbitrary and novel rules) and on the day/night task (in which the output is verbal). Results are consistent, at least, with the hypothesis that children with autism are challenged by executive tasks because they are unlikely to encode rules in a verbal form.

3.1.167. Buitelaar, J.K., van der Wees, M., Swaab-Barneveld, H., van der Gaag, R.J. "Theory of mind and emotion-recognition functioning in autistic spectrum disorders and in psychiatric control and normal children." *Dev Psychopathol* 1999 Winter;11(1):39-58.

University of Utrecht, The Netherlands.

The hypothesis was tested that weak theory of mind (ToM) and/or emotion recognition (ER) abilities are specific to subjects with autism. Differences in ToM and ER performance were examined between autistic ($n = 20$), pervasive developmental disorder-not otherwise specified (PDD-NOS) ($n = 20$), psychiatric control ($n = 20$), and normal children ($n = 20$). The clinical groups were matched person-to-person on age and verbal IQ. We used tasks for the matching and the context recognition of emotional expressions, and a set of first- and second-order ToM tasks. Autistic and PDD-NOS children could not be significantly differentiated from each other, nor could they be differentiated from the psychiatric controls with

a diagnosis of ADHD ($n = 9$). The psychiatric controls with conduct disorder or dysthymia performed about as well as normal children. The variance in second-order ToM performance contributed most to differences between diagnostic groups.

3.1.168. Terai, K., Munesue, T., Hiratani, M. "Excessive water drinking behavior in autism." *Brain Dev* 1999 Mar;21(2):103-6.

Noto Second Hospital (Division of Neuropsychiatry), Nanao, Ishikawa, Japan.

The aim of this study was to determine the incidence of polydipsia in 49 autistic children, and also the influence of psychotropic drugs and residential factors on water drinking behavior, as compared with in 89 mentally retarded children, in schools for mentally handicapped children in Fukui prefecture. Questionnaires were used to detect polydipsia and to assess the severity of the water drinking behavior in the autistic children and mentally retarded children. The incidence of polydipsia in the autistic children tended to be higher ($P = 0.074$) than that in the retarded children. The severity of water drinking behavior was significantly higher in autism ($P = 0.022$) than in mental retardation. The majority of the autistic children with polydipsia had been taking no psychotropic drugs. The incidence of polydipsia showed no significant difference between two residential situations, i.e. 'not at home' and 'at home'. The present study suggests that polydipsia or excessive water drinking behavior occurs more often in autism than in mental retardation, possibly due to some intrinsic factor in autism itself.

3.1.169. Celani, G., Battacchi, M.W., Arcidiacono, L. "The understanding of the emotional meaning of facial expressions in people with autism." *J Autism Dev Disord* 1999 Feb;29(1):57-66. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Psychology, University of Bologna, Italy.

Ten autistic individuals (mean age: 12.7 years, SD 3.8, range 5.10-16.0), 10 Down individuals (12.3 years, SD 3.0, range 7.1-16.0), and a control group of 10 children with normal development (mean age: 6.3 years, SD 1.6, range 4.0-9.4), matched for verbal mental age, were tested on a delayed-matching task and on a sorting-by-preference task. The first task required subjects to match faces on the basis of the emotion being expressed or on the basis of identity. Different from the typical simultaneous matching procedure the target picture was shortly presented (750 msec) and was not visible when the sample pictures were shown to the subject, thus reducing the possible use of perceptual, piecemeal, processing strategies based on the typical features of the emotional facial expression. In the second task, subjects were required to rate the valence of an isolated stimulus, such as facial expression of emotion or an emotional situation in which no people were represented. The aim of the second task was to compare the autistic and nonautistic children's tendency to judge pleasantness of a face using facial expression of emotion as a meaningful index. Results showed a significantly worse

performance in autistic individuals than in both normal and Down subjects on both facial expression of emotion subtasks, although on the identity and emotional situation subtasks there were no significant differences between groups.

3.1.170. Dennis, M., Lockyer, L., Lazenby, A.L., Donnelly, R.E., Wilkinson, M., Schoonheydt, W. "Intelligence patterns among children with high-functioning autism, phenylketonuria, and childhood head injury." *J Autism Dev Disord* 1999 Feb;29(1):5-17. Publication Types: Clinical Trial.

Department of Psychology, Hospital for Sick Children, Toronto, Canada.

High-functioning children with autistic-spectrum disorder show the typical pattern of lower Comprehension relative to their own scores on Block Design. This profile is shared, almost exactly, by age- and IQ-matched children with poorer control PKU. Quite distinct profiles are shown by children with better control PKU, who show no difference between Block Design and Comprehension, and by children with head injury involving frontal lobe contusion, who show slightly better Comprehension than Block Design. The data bear on several questions: the relation between Comprehension deficits and language functions measured by Vocabulary; the limits of the advantages conveyed by higher IQ to autistic individuals; whether impaired Comprehension in autism indexes persisting symptoms and/or impairments on theory of mind tasks; the possibility that dopamine deficiency is common to autism and poorer control PKU; and the need for future research aimed at understanding the relations among neurodevelopmental disorders.

3.1.171. Bolte, S., Dickhut, H., Poustka, F. "Patterns of parent-reported problems indicative in autism." *Psychopathology* 1999 Mar-Apr;32(2):93-7.

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Parental report Child Behavior Checklists (CBCL) of 77 male and female subjects aged 4-18 years were analyzed in this study. Individuals had been given diagnoses of autistic disorder using the Autism Diagnostic-Interview-Revised (ADI-R) within a research project on the genetics of autism. A feature of behavior problems independent of sex but influenced by age and IQ level could be identified for the autistic sample with highest relative scores on the scales measuring attention problems, social problems and thought problems and low scores on the scale for somatic complaints.

3.1.172. Hollander, E., DelGiudice-Asch, G., Simon, L., Schmeidler, J., Cartwright, C., DeCaria, C.M., Kwon, J., Cunningham-Rundles, C., Chapman, F., Zabriskie, J.B. "B lymphocyte antigen D8/17 and repetitive behaviors in autism." *Am J Psychiatry* 1999 Feb;156(2):317-20.

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OBJECTIVE: Monoclonal antibody D8/17 identifies a B lymphocyte antigen with expanded expression in rheumatic fever, Sydenham's chorea, and subgroups of obsessive-compulsive disorder and Tourette's syndrome with repetitive behaviors. The authors examined the rate of D8/17 expression in children with autism and its correlation with severity of repetitive behaviors. **METHOD:** Blood samples from 18 patients with autism and 14 comparable medically ill children were evaluated for percentage of D8/17-positive B cells by immunofluorescence and for streptococcal antibodies. Severity of repetitive behaviors was also determined. **RESULTS:** The frequency of individuals with > or =11% D8/17-positive cells was significantly higher in the autistic patients (78%) than the comparison subjects (21%), severity of repetitive behaviors significantly correlated with D8/17 expression, and D8/17-positive patients had significantly higher compulsion scores than D8/17-negative patients. **CONCLUSIONS:** D8/17 expression is high in patients with autism and may serve as a marker for compulsion severity within autism.

3.1.173. Newell, K.M., Sprague, R.L., Pain, M.T., Deutsch, K.M., Meinhold, P. "Dynamics of self-injurious behaviors." *Am J Ment Retard* 1999 Jan;104(1):11-21.

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Self-injurious behavior was examined in a case study of head-banging by an 8-year-old girl with profound mental retardation and an autistic disorder. Trajectories of the arm movements and impact forces of the head blows were determined from a dynamic analysis of videotapes. Results revealed a high degree of cycle-to-cycle consistency in the qualitative dynamics of the limb motions, with one hand motions being faster than those with two hands (inphase and antiphase) and the motions with the helmet about 25% faster than those without the helmet. The impact force of SIBs as a percentage of body weights are near the low end of forces generated in boxing blows and karate hits.

3.1.174. Mottron, L., Belleville, S., Stip, E., Morasse, K. "Atypical memory performance in an autistic savant." *Memory* 1998 Nov;6(6):593-607.

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This study explored the mechanisms underlying the hypermnesia of an autistic savant (NM) through three experiments. The first two served to assess whether absence of interference was responsible for NM's exceptional list memory. The third investigated the type of cues used in recall. Results indicated absence of retroactive interference but presence of slight proactive interference in list recall of proper names. Normal interference effects were found, however, in list recall of common nouns. Exceptional performance was also demonstrated in a missing-name task involving spatial and verbal recall cues. The findings suggest that the outstanding episodic memory presented by some savant persons with autism might be related to an abnormally high resistance to interference.

3.1.175. Pascualvaca, D.M., Fantie, B.D., Papageorgiou, M., Mirsky, A.F. "Attentional capacities in children with autism: is there a general deficit in shifting focus?" *J Autism Dev Disord* 1998 Dec;28(6):467-78.

Section on Clinical and Experimental Neuropsychology, National Institute of Mental Health, Bethesda, Maryland 20892-1366, USA.

Twenty-three children with autism and two control groups completed an attention battery comprising three versions of the continuous performance test (CPT), a digit cancellation task, the Wisconsin Card Sorting Test (WCST), and two novel, computerized tests of shifting attention (i.e., the Same-Different Computerized Task and the Computerized Matching Task). Children with autism could focus on a particular stimulus and sustain this focus as indicated by their performance on the digit cancellation task and the CPT. Their performance on the WCST suggested problems in some aspects of shifting attention (i.e., disengaging attention). The autism group performed as well as controls on the Same-Different Computerized Task, however, that required successive comparisons between stimuli. This implies that they could, in fact, shift their attention continuously. In addition, they did not differ from controls on the Computerized Matching Task, an analog of the WCST, suggesting that they do not have a general deficit in shifting attention.

3.1.176. Corona, R., Dissanayake, C., Arbellé, S., Wellington, P., Sigman, M. "Is affect aversive to young children with autism? Behavioral and cardiac responses to experimenter distress." *Child Dev* 1998 Dec;69(6):1494-502.

University of California, Los Angeles, USA.

The aim of this study was to determine whether displays of negative emotions are more aversive to young children with autism than displays of neutral emotions. The attention, behavioral reactions, facial affect, and cardiac responses of 22 autistic and 22 mentally retarded 3-5-year-old children were compared when an experimenter pretended to hurt herself and showed strong distress in contrast to when the experimenter pretended to hurt herself but showed only neutral affect. The children in both diagnostic groups looked more at the experimenter and appeared more interested and concerned when she displayed strong distress than when she showed neutral affect. The heart rate of the mentally retarded children decreased during the distress condition relative to a baseline condition, but the heart rate of the children with autism did not change across conditions. In summary, the children with autism gave no evidence of being overly aroused by or avoiding the distressed experimenter.

3.1.177. Leekam, S.R., Hunnisett, E., Moore, C. "Targets and cues: gaze-following in children with autism." *J Child Psychol Psychiatry* 1998 Oct;39(7):951-62. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Psychology, University of Kent, Canterbury, UK.

Children with autism are known to have difficulties in sharing attention with others. Yet one joint attention behaviour, the ability to follow another person's head turn and gaze direction, may be achieved without necessarily sharing attention. Why, then, should autistic children have difficulties with it? In this study we examined the extent of this difficulty by testing school-aged autistic children across three different contexts; experiment, observation, and parent interview. We also tested whether the ability to orient to another person's head and gaze could be facilitated by increasing children's attention to environmental targets and social cues. Results for experiment and observation demonstrate that a sizeable proportion of children with autism did not have difficulties with following another's head turn. There was a difference between children with high and low verbal mental ages, however. Whereas children with higher mental ages (over 48 months) were able to orient spontaneously to another person's head turn, children with lower mental ages had difficulties with this response. When cues were added (pointing, language) or when feedback from targets was given, however, their performance improved. Parent interview data indicated that children with autism, whatever their mental age, began to follow head turn and gaze direction years later than typically developing children. Developments in attention and language are proposed as possible factors to account for this developmental delay.

3.1.178. Williams, J.H., Whiten, A., Suddendorf, T., Perrett, D.I. "Imitation, mirror neurons and autism." Publication Types: Review, Review, Tutorial.

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Various deficits in the cognitive functioning of people with autism have been documented in recent years but these provide only partial explanations for the condition. We focus instead on an imitative disturbance involving difficulties both in copying actions and in inhibiting more stereotyped mimicking, such as echolalia. A candidate for the neural basis of this disturbance may be found in a recently discovered class of neurons in frontal cortex, 'mirror neurons' (MNs). These neurons show activity in relation both to specific actions performed by self and matching actions performed by others, providing a potential bridge between minds. MN systems exist in primates without imitative and 'theory of mind' abilities and we suggest that in order for them to have become utilized to perform social cognitive functions, sophisticated cortical neuronal systems have evolved in which MNs function as key elements. Early developmental failures of MN systems are likely to result in a consequent cascade of developmental impairments characterised by the clinical syndrome of autism.

MANIFESTATION

Biological

3.2.1. Courchesne, E., Carper, R., Akshoomoff, N. "Evidence of brain overgrowth in the first year of life in autism." *JAMA*. 2003 Jul 16;290(3):337-44.

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CONTEXT: Autism most commonly appears by 2 to 3 years of life, at which time the brain is already abnormally large. This raises the possibility that brain overgrowth begins much earlier, perhaps before the first clinically noticeable behavioral symptoms. OBJECTIVES: To determine whether pathological brain overgrowth precedes the first clinical signs of autism spectrum disorder (ASD) and whether the rate of overgrowth during the first year is related to neuroanatomical and clinical outcome in early childhood. DESIGN, SETTING, AND PARTICIPANTS: Head circumference (HC), body length, and body weight measurements during the first year were obtained from the medical records of 48 children with ASD aged 2 to 5 years who had participated in magnetic resonance imaging studies. Of these children, 15 (longitudinal group) had measurements at 4 periods during infancy: birth, 1 to 2 months, 3 to 5 months, and 6 to 14 months; and 33 (partial HC data group) had measurements at birth and 6 to 14 months ($n = 7$), and at birth only ($n = 28$). MAIN OUTCOME MEASURES: Age-related changes in infants with ASD who had multiple-age measurements, and the relationship of these changes to brain anatomy and clinical and diagnostic outcome at 2 to 5 years were evaluated by using 2 nationally recognized normative databases: cross-sectional normative data from a national survey and longitudinal data of individual growth. RESULTS: Compared with normative data of healthy infants, birth HC in infants with ASD was significantly smaller ($z = -0.66$, $P < .001$); after birth, HC increased 1.67 SDs and mean HC was at the 84th percentile by 6 to 14 months. Birth HC was related to cerebellar gray matter volume at 2 to 5 years, although the excessive increase in HC between birth and 6 to 14 months was related to greater cerebral cortex volume at 2 to 5 years. Within the ASD group, every child with autistic disorder had a greater increase in HC between birth and 6 to 14 months (mean [SD], 2.19 [0.98]) than infants with pervasive developmental disorder-not otherwise specified (0.58 [0.35]). Only 6% of the individual healthy infants in the longitudinal data showed accelerated HC growth trajectories (>2.0 SDs) from birth to 6 to 14 months; 59% of infants with autistic disorder showed these accelerated growth trajectories. CONCLUSIONS: The clinical onset of autism appears to be preceded by 2 phases of brain growth abnormality: a reduced head size at birth and a sudden and excessive increase in head size between 1 to 2 months and 6 to 14 months. Abnormally accelerated rate of growth may serve as an early warning signal of risk for autism.

3.2.2. Levitt, J.G., Blanton, R.E., Smalley, S., Thompson, P.M., Guthrie, D., McCracken, J.T., Sadoun, T., Heinichen, L., Toga, A.W. "Cortical sulcal maps in autism." *Cereb Cortex*. 2003 Jul;13(7):728-35. Publication Types: Clinical Trial, Controlled Clinical Trial.

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This study presents the first three-dimensional mapping of cortical sulcal patterns in autism, a pervasive developmental disorder, the underlying neurobiology of which remains unknown. High-resolution T(1)-weighted MRI scans were acquired in 21 autistic (age 10.7 +/- 3.1 years) and 20 normal control (age 11.3 +/- 2.9) children and adolescents. Using parametric mesh-based analytic techniques, we created three-dimensional models of the cerebral cortex and detailed maps of 22 major sulci in stereotaxic space. These average maps revealed anatomic shifting of major sulci primarily in frontal and temporal areas. Specifically, we found anterior and superior shifting of the superior frontal sulci bilaterally ($P < \text{or} = 0.0003$), anterior shifting of the right Sylvian fissure ($P = 0.0002$), the superior temporal sulcus ($P = 0.0006$ right, $P = 0.02$ left) and the left inferior frontal sulcus ($P < \text{or} = 0.002$) in the autistic group relative to the normal group. Less significant sulcal shifts occurred in the intraparietal and collateral sulci. These findings may indicate delayed maturation in autistic subjects in these brain regions involved in functions including working memory, emotion processing, language and eye gaze.

3.2.3. Filipek, P.A., Juranek, J., Smith, M., Mays, L.Z., Ramos, E.R., Bocian, M., Masser-Frye, D., Laulhere, T.M., Modahl, C., Spence, M.A., Gargus, J.J. "Mitochondrial dysfunction in autistic patients with 15q inverted duplication." *Ann Neurol*. 2003 Jun;53(6):801-4.

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Two autistic children with a chromosome 15q11-q13 inverted duplication are presented. Both had uneventful perinatal courses, normal electroencephalogram and magnetic resonance imaging scans, moderate motor delay, lethargy, severe hypotonia, and modest lactic acidosis. Both had muscle mitochondrial enzyme assays that showed a pronounced mitochondrial hyperproliferation and a partial respiratory chain block most parsimoniously placed at the level of complex III, suggesting candidate gene loci for autism within the critical region may affect pathways influencing mitochondrial function.

3.2.4. White, J.F. "Intestinal pathophysiology in autism." *Exp Biol Med (Maywood)*. 2003 Jun;228(6):639-49. Publication Types: Review, Review Literature.

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Autism is a life-long developmental disorder affecting as many as 1 in 500 children. The causes for this profound disorder are largely unknown. Recent research has uncovered pathology in the gastrointestinal tract of autistic children. The pathology, reported to extend from the esophagus to the colon, is described here along with other studies pointing to a connection between diet and the severity of symptoms expressed in autism. The evidence that there is impaired intestinal permeability in autism is reviewed, and various theories are discussed by which a leaky gut could develop. Lastly, some possible ways in which impaired gastrointestinal function might influence brain function are discussed.

3.2.5. Aldred, S., Moore, K.M., Fitzgerald, M., Waring, R.H. "Plasma amino acid levels in children with autism and their families." *J Autism Dev Disord.* 2003 Feb;33(1):93-7.

Pharmaceutical Sciences Research Institute, Aston University, Birmingham, B4 7ET, United Kingdom.

Plasma amino acid levels were measured in autistic and Asperger syndrome patients, their siblings, and parents. The results were compared with values from age-matched controls. Patients with autism or Asperger syndrome and their siblings and parents all had raised glutamic acid, phenylalanine, asparagine, tyrosine, alanine, and lysine ($p < .05$) than controls, with reduced plasma glutamine. Other amino acids were at normal levels. These results show that children with autistic spectrum disorders come from a family background of dysregulated amino acid metabolism and provide further evidence for an underlying biochemical basis for the condition.

3.2.6. Herbert, M.R., Ziegler, D.A., Deutsch, C.K., O'Brien, L.M., Lange, N., Bakardjiev, A., Hodgson, J., Adrien, K.T., Steele, S., Makris, N., Kennedy, D., Harris, G.J., Caviness, V.S. Jr. "Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys." *Brain.* 2003 May;126(Pt 5):1182-92.

Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA. mherbert1@partners.org

High-functioning autistic and normal school-age boys were compared using a whole-brain morphometric profile that includes both total brain volume and volumes of all major brain regions. We performed MRI-based morphometric analysis on the brains of 17 autistic and 15 control subjects, all male with normal intelligence, aged 7-11 years. Clinical neuroradiologists judged the brains of all subjects to be clinically normal. The entire brain was segmented into cerebrum, cerebellum, brainstem and ventricles. The cerebrum was subdivided into cerebral cortex, cerebral white matter, hippocampus-amygdala, caudate nucleus, globus pallidus plus putamen, and diencephalon (thalamus plus ventral diencephalon). Volumes were derived for each region and compared between groups both before and after adjustment for variation in total brain volume. Factor analysis was then used to group brain regions based on their intercorrelations. Volumes were significantly different between groups overall; and diencephalon, cerebral white matter, cerebellum and globus pallidus-putamen were significantly larger in the autistic group. Brain volumes were not significantly different overall after adjustment for total brain size, but this analysis approached significance and effect sizes and univariate comparisons remained notable for three regions, although not all in the same direction: cerebral white matter showed a trend towards being disproportionately larger in autistic boys, while cerebral cortex and hippocampus-amygdala showed trends toward being disproportionately smaller. Factor analysis of all brain region volumes yielded three factors, with central white matter grouping alone, and with cerebral cortex and hippocampus-amygdala grouping separately from other grey

matter regions. This morphometric profile of the autistic brain suggests that there is an overall increase in brain volumes compared with controls. Additionally, results suggest that there may be differential effects driving white matter to be larger and cerebral cortex and hippocampus-amygdala to be relatively smaller in the autistic than in the typically developing brain. The cause of this apparent dissociation of cerebral cortical regions from subcortical regions and of cortical white from grey matter is unknown, and merits further investigation.

3.2.7. Salmond, C.H., de Haan, M., Friston, K.J., Gadian, D.G., Vargha-Khadem, F. "Investigating individual differences in brain abnormalities in autism." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):405-13.

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Autism is a psychiatric syndrome characterized by impairments in three domains: social interaction, communication, and restricted and repetitive behaviours and interests. Recent findings implicate the amygdala in the neurobiology of autism. In this paper, we report the results of a series of novel experimental investigations focusing on the structure and function of the amygdala in a group of children with autism. The first section attempts to determine if abnormality of the amygdala can be identified in an individual using magnetic resonance imaging in vivo. Using single-case voxel-based morphometric analyses, abnormality in the amygdala was detected in half the children with autism. Abnormalities in other regions were also found. In the second section, emotional modulation of the startle response was investigated in the group of autistic children. Surprisingly, there were no significant differences between the patterns of emotional modulation of the startle response in the autistic group compared with the controls.

3.2.8. Reichelt, K.L., Knivsberg, A.M. "Can the pathophysiology of autism be explained by the nature of the discovered urine peptides?" *Nutr Neurosci.* 2003 Feb;6(1):19-28. Publication Types: Review, Review, Tutorial.

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Opioid peptides derived from food proteins (exorphins) have been found in urine of autistic patients. Based on the work of several groups, we try to show that exorphins and serotonin uptake stimulating factors may explain many of the signs and symptoms seen in autistic disorders. The individual symptoms ought to be explainable by the properties and behavioural effects of the found peptides. The data presented form the basis of an autism model, where we suggest that exorphins and serotonin uptake modulators are key mediators for the development of autism. This may be due to a genetically based peptidase deficiency in at least two or more peptidases and, or of peptidase regulating proteins made manifest by a dietary overload of exorphin precursors such as by increased gut uptake.

3.2.9. Tsatsanis, K.D., Rourke, B.P., Klin, A., Volkmar, F.R., Cicchetti, D., Schultz, R.T. "Reduced thalamic volume in high-functioning individuals with autism." *Biol Psychiatry*. 2003 Jan 15;53(2):121-9.

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BACKGROUND: In this study, specific consideration is given to a role for the thalamus in autism. **METHODS:** A volumetric analysis of the thalamus was conducted using magnetic resonance imaging, based on segmentation of continuous 1.2 mm(3) coronal images. The sample consisted of 12 high-functioning individuals with autism, mean age of 21.0 years (SD = 10.4) and mean IQ of 106.4 (SD = 18.3). Normal control subjects were selected to match this group; the mean age was 18.1 years (SD = 6.3); mean IQ was 108.8 (SD = 15.6). **RESULTS:** Unadjusted mean thalamic volume was not significantly different; however, there were significant differences in the relationship between thalamic volume and total brain volume (TBV). The correlation was strong and positive in the control group but statistically nonsignificant in the autism group. Group differences were found when adjustments were made for TBV, achieved by grouping subjects' measurements on this variable using a split median procedure. Mean thalamic volume was significantly reduced in the autism group relative to normal control subjects, specifically within the high TBV group. **CONCLUSION:** The increase in thalamic volume with increase in TBV was not seen in autism, suggesting underdeveloped connections between cortical and subcortical regions and indicating a need to examine this structure further.

3.2.10. Friedman, S.D., Shaw, D.W., Artru, A.A., Richards, T.L., Gardner, J., Dawson, G., Posse, S., Dager, S.R. "Regional brain chemical alterations in young children with autism spectrum disorder." *Neurology*. 2003 Jan 14;60(1):100-7. Publication Types: Clinical Trial, Controlled Clinical Trial.

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OBJECTIVE: The authors evaluated regional brain chemistry for evidence of increased neuronal packing density in autism. **METHODS:** Forty-five 3- to 4-year-old children with autism spectrum disorder (ASD), 13 children with typical development (TD), and 15 children with delayed development (DD) were studied using dual-echo proton echoplanar spectroscopic imaging (32 x 32 matrix-1 cm(3) voxels) to measure brain chemical concentrations and relaxation times. Chemical quantification was corrected for tissue partial volume and relative measures of chemical relaxation (T(2r)) were calculated from the paired echoes. Measures from averaged and individual regions were compared using analysis of variance corrected for multiple comparisons. **RESULTS:** ASD subjects demonstrated reduced N-acetylaspartate (NAA) (-10%), creatine (Cre) (-8%), and myo-inositol (-13%) concentrations compared to TD controls and prolonged NAA T(2r) relative to TD (7%) and DD (9%) groups. Compared to DD subjects, children with ASD also demonstrated prolonged T(2r) for choline (10%) and Cre (9%). Regional analyses demonstrated subtle patterns of chemical alterations in ASD compared to the TD and DD groups.

CONCLUSIONS: Brain chemical abnormalities are present in ASD at 3 to 4 years of age. However, the direction and widespread distribution of these abnormalities do not support hypothesis of diffuse increased neuronal packing density in ASD.

3.2.11. Walz, N.C., Byars, A.W., Egelhoff, J.C., Franz, D.N. "Supratentorial tuber location and autism in tuberous sclerosis complex." *J Child Neurol*. 2002 Nov;17(11):830-2.

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The high rate of autism in tuberous sclerosis complex provides an opportunity to study the pathogenesis of autism. This study investigated the relationship between a DSM-IV diagnosis of autism and tuber location in a sample of 50 individuals with tuberous sclerosis complex. Chi-square analyses revealed no differences between individuals with autism (n = 15) and those without autism (n = 35) on the occurrence of tubers in the right or left frontal, occipital, parietal, or temporal regions. There were no differences between the two groups in the occurrence of tubers in subcortical or cortical regions. In the largest sample to date, these results fail to support the hypothesis that supratentorial tuber location is a marker for autism.

3.2.12. Casanova, M.F., Buxhoeveden, D.P., Brown, C. "Clinical and macroscopic correlates of minicolumnar pathology in autism." *J Child Neurol*. 2002 Sep;17(9):692-5.

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All subcortical arrangements are primarily nuclear in type. The cortex has been the first part of the brain to evolve a radial and laminar arrangement of cells. The resultant modular arrangement is based on the cell minicolumn: a self-contained ecosystem of connectivity linking afferent, efferent, and interneuronal connections. Recently, the cell minicolumn has been found to be abnormal in patients with autism. This article relates different aspects of the cell minicolumn and larger-scale neuronal assemblies to potential research techniques and their application to clinical practice.

3.2.13. Puri, B.K., Singh, I. "Normal phospholipid-related signal transduction in autism." *Prog Neuropsychopharmacol Biol Psychiatry*. 2002 Dec;26(7-8):1405-7.

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The aim of this study was to test the hypothesis that autism (a neurodevelopmental disorder of unknown etiology) is associated with altered phospholipid-related signal transduction using the niacin skin flush test. This is the first reported use of this test in this disorder. The response to topical aqueous methyl nicotinate solution was recorded at 5-min intervals over 20 min in eight patients with autism and in 16 age- and sex-matched normal individuals with no history

of this or any other major neuropsychiatric disorder. There was no significant difference between the mean volumetric niacin response (VNR) (+/- S.E.M.) in the patients with autism, 27.0 (+/- 2.2) mol s l(-1), and the mean VNR of 27.6 (+/- 2.4) mol s l(-1) in the control group ($P>.8$). Therefore, there appears to be no evidence of altered phospholipid-related signal transduction in autism as assessed by this test. Furthermore, since the VNR is reduced in a related disorder, schizophrenia, these results suggest fatty acid abnormalities in autism are likely to differ from those in schizophrenia.

3.2.14. Coutinho, M.B., Rocha, V., Santos, M.C. "Auditory brainstem response in two children with autism." *Int J Pediatr Otorhinolaryngol* 2002 Oct 21;66(1):81-5.

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Autism develops before 30 months of age. Autistic disorder is characterized by a qualitative impairment in verbal and non verbal communication, in imaginative activity, and in reciprocal social interactions. Communication in autism is so strikingly impaired that the function of the hearing system has been under study over the past 30 years, namely after the advent of physiological assessment of hearing with the auditory brainstem response (ABR). Many research studies were developed to study ABR in autism as they constitute a direct test of both hearing status and integrity of brainstem pathways, but the results obtained are contradictory. The authors present case reports of two children with autistic disorder, 2 and 4 years of age, in which the ABR findings document a prevalent Peak I in the four ears tested. This characteristic configuration in ABR has not been previously reported and future work is needed to establish the importance of this finding and its implications in the awareness of the auditory status in these children.

3.2.15. Horvath, K., Perman, J.A. "Autistic disorder and gastrointestinal disease." *Curr Opin Pediatr* 2002 Oct;14(5):583-7. Publication Types: Review, Review, Tutorial.

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Autistic disorder is a pervasive developmental disorder manifested in the first 3 years of life by dysfunction in social interaction and communication. Many efforts have been made to explore the biologic basis of this disorder, but the etiology remains unknown. Recent publications describing upper gastrointestinal abnormalities and ileocolitis have focused attention on gastrointestinal function and morphology in these children. High prevalence of histologic abnormalities in the esophagus, stomach, small intestine and colon, and dysfunction of liver conjugation capacity and intestinal permeability were reported. Three surveys conducted in the United States described high prevalence of gastrointestinal symptoms in children with autistic disorder. Treatment of the digestive problems may have positive effects on their behavior.

3.2.16. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E. "Neuronal density and architecture (Gray Level Index) in the brains of autistic patients." *J Child Neurol* 2002 Jul;17(7):515-21.

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Although neuropathologic studies have centered on small samples, it is accepted that brains of autistic individuals tend to be large, on average. Knowledge regarding the cause of this macrocephaly is limited. Postmortem studies reveal little in terms of cortical dysplasia. Some of these studies suggest increased cell-packing density in subcortical structures. These neuronormometric studies have been subjective or based their conclusions on measures of neuronal density. Our study sought the possible presence of increased cell-packing density by using the Gray Level Index. The Gray Level Index is defined as the ratio of the area covered by Nissl-stained elements to unstained area in postmortem samples. Analyzed images included Brodmann's cortical areas 9, 21, and 22 of 9 autistic patients (7 males, 2 females; mean age of 12 years, with a range of 5 to 28 years) and 11 normal controls (7 males, 4 females; mean age of 14 years, with a range of 3 to 25 years). The overall multivariate test revealed significant differences both between autistic patients and controls ($P = .001$) and between hemispheres ($P = .025$). Follow-up univariate tests showed significant diagnosis-dependent effects in feature distance ($P = .005$), the standard deviation in distance ($P = .016$), and feature amplitude ($P = .001$). The overall mean Gray Level Index was 19.4% in controls and 18.7% in autism ($P = .724$). In autism, an increased number of minicolumns, combined with fewer cells per column (or their greater dispersion), results in no global difference in neuronal density.

3.2.17. Gomot, M., Giard, M.H., Adrien, J.L., Barthelemy, C., Bruneau, N. "Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning." *Psychophysiology* 2002 Sep;39(5):577-84. Publication Types: Clinical Trial.

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Exaggerated reactions to even small changes in the environment and abnormal behaviors in response to auditory stimuli are frequently observed in children with autism (CWA). Brain mechanisms involved in the automatic detection of auditory frequency change were studied using scalp potential and scalp current density (SCD) mapping of mismatch negativity (MMN) in 15 CWA matched with 15 healthy children. Compared with the response in controls, MMN recorded at the Fz site in CWA showed significantly shorter latency and was followed by a P3a wave. Mapping of potentials indicated significant intergroup differences. Moreover, SCD mapping demonstrated the dynamics of the different MMN generators: Although temporal component was evidenced bilaterally in both groups, it occurred earlier on the left hemisphere in CWA, preceded by an abnormal early left frontal component. The electrophysiological pattern reported here emphasized a left frontal cortex dysfunctioning

that might also be implicated in cognitive and behavioral impairment characteristic of this complex neurodevelopmental disorder.

3.2.18. Anderson, G.M., Gutknecht, L., Cohen, D.J., Brailly-Tabard, S., Cohen, J.H., Ferrari, P., Roubertoux, P.L., Tordjman, S. "Serotonin transporter promoter variants in autism: functional effects and relationship to platelet hyperserotonemia." *Mol Psychiatry* 2002;7(8):831-6.

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The well-replicated platelet hyperserotonemia of autism has stimulated interest in serotonin (5-HT) in autism. We have examined the effects of the serotonin transporter gene (5-HTT, locus SLC6A4) promoter polymorphism (5-HTTLPR) on platelet 5-HT physiology in autism. Platelet 5-HT uptake rates and affinities ($V(\max)$ and $K(m)$), uptake site densities ($B(\max)$) and 5-HT levels were examined in 31 French individuals with autism genotyped with respect to the 5-HTTLPR. Platelet 5-HT uptake and 5-HT levels were measured using HPLC; uptake sites were determined by radioligand binding. A 1.5-fold increased rate ($V(\max)$) of platelet 5-HT uptake was observed in ll genotype individuals compared to those with ls and ss genotypes (Mann-Whitney U-test, $P = 0.022$). However, no significant relationship was observed between genotype and uptake site density (U-test, $P = 0.51$). Although median levels of platelet 5-HT in platelet-rich plasma were higher in the ll group, only trend level significance was observed (U-test, $P = 0.069$); platelet 5-HT content measured in whole blood was similar across genotypes. Uptake rates were well correlated with $B(\max)$ values ($r = 0.66$, $P = 0.002$); correlations between uptake and platelet 5-HT levels and between $B(\max)$ values and 5-HT levels were somewhat lower. While 5-HTTLPR alleles had an appreciable effect on platelet 5-HT uptake rates, effects on 5-HT levels and uptake site density were smaller or absent. Based on these preliminary data and prior studies of allele frequencies, we conclude that the 5-HTTLPR is not a major determinant of the group mean platelet serotonin elevation seen in autism. However, a role for increased uptake in the hyperserotonemia of autism can not be ruled out. In addition, it appears that studies of platelet 5-HT measures in autism and other disorders should take account of the effects of 5-HTTLPR genotype on 5-HT uptake

3.2.19. Wilcox, J., Tsuang, M.T., Ledger, E., Algeo, J., Schnurr, T. "Brain perfusion in autism varies with age." *Neuropsychobiology* 2002;46(1):13-6.

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Our subjects consisted of 14 autistic individuals and 14 controls ranging in age from 3 to 37 years. A (99m)Tc HMPAO single photon emission computed tomogram (SPECT) was used to examine blood flow variations between autistic subjects, compared to an age- and gender-matched control group. We found significant hypoperfusion in the prefrontal

areas of autistic individuals as compared to normals in every case ($p < 0.01$). As the age of the autistic individuals increased the hypoperfusion of verbal-associated areas in the left temporal lobe and frontal areas became more evident. The findings were significant at the $p < 0.001$ level. The changes in perfusion over time correlated with language development and acquisition as individuals matured. We conclude that autistic individuals have a deficiency in prefrontal areas associated with word identification and language formation skills. This subsequently prevents development of true verbal fluency and development in the temporal and frontal areas associated with speech and communication. Copyright 2002 S. Karger AG, Basel

3.2.20. Villemagne, P.M., Naidu, S., Villemagne, V.L., Yaster, M., Wagner, H.N.Jr., Harris, J.C., Moser, H.W., Johnston, M.V., Darnalls, R.F., Wong, D.F. "Brain glucose metabolism in Rett Syndrome." *Pediatr Neurol* 2002 Aug;27(2):117-22.

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Rett syndrome is a progressive neurologic disorder affecting girls in early childhood with loss of achieved psychomotor abilities and mental retardation. Six sedated female patients (4 to 15 years of age) with a diagnosis of Rett syndrome were studied with [(18)F]fluorodeoxyglucose (FDG) and underwent positron emission tomography scanning of the brain. Relative tracer concentrations between different areas of the brain were assessed, and results were compared with 18 age-matched control subjects. Patients were divided into two age groups: 3 to 8 years of age and 9 to 15 years of age. A relative decrease in [(18)F]FDG uptake in the lateral occipital areas in relation with the whole brain and a relative increase in the cerebellum was evident in both age groups ($P < 0.001$, unpaired Student t test). A relative increase in frontal tracer uptake was observed in the younger group. Sensorimotor areas and relations between cortical and subcortical structures were preserved in all patients. Changes in glucose cerebral metabolism resemble the regional distribution of normal children less than 1 year of age, likely reflecting a maturational arrest. Changes in frontal areas parallel those in postmortem N-methyl-D-aspartate receptor densities and could correlate with different clinical stages of the disease. This pattern differs from those described in Down syndrome, autism, and Alzheimer's disease.

3.2.21. Heilstedt, H.A., Shahbazian, M.D., Lee, B. "Infantile hypotonia as a presentation of Rett syndrome." *Am J Med Genet* 2002 Aug 15;111(3):238-42.

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Rett syndrome (RTT) is classically defined by meeting certain clinical diagnostic criteria. It affects mostly females, and one possible pathogenic mechanism was considered to involve mitochondrial function. This was based on the finding of ultrastructural alterations in the mitochondria and decreased respiratory chain enzyme activity. However, the principal etiology of RTT has since been found to be mutations in the

MECP2 gene, which is located on the X chromosome. Molecular analysis has allowed the phenotype of MECP2 mutations to be broadened beyond RTT to include girls who have mild mental retardation, autism, and an Angelman syndrome phenotype, as well as males with severe encephalopathy. We present a girl with a previously described mutation in the MECP2 gene whose phenotype is of atypical RTT. She presented with hypotonia and developmental delay in infancy without a clear period of normal development. As part of her evaluation for hypotonia, a muscle biopsy and respiratory chain enzyme analysis showed a slight decrease in respiratory chain enzyme activity consistent with previous reports. This report supports broadening the phenotype of patients who should be considered for MECP2 mutation analysis to include cases of developmental delay and hypotonia without evidence of an initial period of normal development. Furthermore, it supports the hypothesis of an underlying secondary defect in energy metabolism contributing to the pathogenesis of RTT. Copyright 2002 Wiley-Liss, Inc.

3.2.22. Kern, J.K. "The possible role of the cerebellum in autism/PDD: disruption of a multisensory feedback loop." *Med Hypotheses* 2002 Sep;59(3):255-60. Publication Types: Review, Review, Tutorial.

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Autism and pervasive developmental disorder (PDD) are characterized by impairments in socialization and communication, and by restricted and stereotypic patterns of behavior. Associated symptoms or features of autism/PDD include problems with attention and orientation, and an odd response to the environment and sensory stimuli. Persons with autism/PDD can over or under respond or react to sensation. Evidence suggests that there is aberrant brain structure in this disorder, particularly in the cerebellum. This paper will attempt to show a possible relationship between the pathology in the cerebellum and the symptomatology seen in autism/PDD with an emphasis on the sensory issues.

3.2.23. Goldberg, M.C., Lasker, A.G., Zee, D.S., Garth, E., Tien, A., Landa, R.J. "Deficits in the initiation of eye movements in the absence of a visual target in adolescents with high functioning autism." *Neuropsychologia* 2002;40(12):2039-49. Publication Types: Clinical Trial.

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BACKGROUND: We used ocular motor paradigms to examine whether or not saccades are impaired in individuals with high functioning autism (HFA). **METHODS:** We recorded eye movements in patients with HFA (n=11), and in normal adolescents (n=11) on anti-saccade, memory-guided saccade (MGS), predictive saccade and gap/overlap tasks. **RESULTS:** Compared with the normal subjects, patients with HFA had

(1) a significantly higher percentage of directional errors on the anti-saccade task (63.2% versus 26.6%), (2) a significantly higher percentage of response suppression errors on a MGS task (60.3% versus 29.5%) and (3) a significantly lower percentage of predictive eye movements on a predictive saccade task. They also showed longer latencies on a MGS task and for all conditions tested on a gap/null/overlap task (fixation target extinguished before, simultaneously, or after the new peripheral target appeared). When the latencies during the gap condition were subtracted from the latencies in the overlap condition, there was no difference between patients and normals. **CONCLUSIONS:** Abnormalities in ocular motor function in patients with HFA provide preliminary evidence for involvement of a number of brain regions in HFA including the dorsolateral prefrontal cortex (dlPFC) and the frontal eye fields (FEFs) and possibly the basal ganglia and parietal lobes.

3.2.24. Carper, R.A., Moses, P., Tigue, Z.D., Courchesne, E. "Cerebral lobes in autism: early hyperplasia and abnormal age effects." *Neuroimage* 2002 Aug;16(4):1038-51.

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Metabolic, functional, behavioral, and histologic studies suggest that the structure of the cerebrum may be abnormal in autism. In a previous cross-sectional study we found abnormal enlargement of cerebral cortex and cerebral white matter volumes in autistic 2- and 3-year-olds and abnormally slow rates of volume change across later ages. In the present study, we assessed whether these volume abnormalities are limited to particular cerebral regions or are pervasive throughout the cerebrum. We used magnetic resonance imaging (MRI) to quantify volumes of cerebral lobes (frontal, temporal, parietal, and occipital regions), using classic sulcal boundaries to define regions. We examined 38 boys with autism and 39 normal control boys between the ages of 2 and 11 years. Several regions showed signs of gray matter and white matter hyperplasia in 2- and 3-year-old patients (as much as 20% enlargement), but there appeared to be an anterior to posterior gradient in the degree of hyperplasia. The frontal lobe showed the greatest enlargement while the occipital lobe was not significantly different from normal. Gray and white matter differences were not found in the older children. By examining the relationships between regional volumes and subject age, we found that frontal, temporal, and parietal white matter volumes, as well as frontal and temporal gray matter volumes, changed at significantly slower rates in autism patients than in controls across the 2- to 11-year-age range. For example, frontal lobe white matter volume increased by about 45% from 2-4 years of age to 9-11.5 years, but by only 13% in autistic patients. Mechanisms that might account for early hyperplasia are discussed as they might relate to the regional differences in degree of abnormality. For instance, possible influences of neurotrophic factors, or of abnormal afferent activity from other affected brain regions are considered.

3.2.25. Black, C., Kaye, J.A., Jick, H. "Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database." *BMJ* 2002 Aug 24;325(7361):419-21.

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OBJECTIVES: To assess whether children with autism are more likely to have a history of gastrointestinal disorders than children without autism. **DESIGN:** Nested case-control study. **SETTING:** UK General Practice Research Database. **SUBJECTS:** Children born after 1 January 1988 and registered with the General Practice Research Database within 6 months of birth. **OUTCOME MEASURES:** Chronic inflammation of the gastrointestinal tract, coeliac disease, food intolerance, and recurrent gastrointestinal symptoms recorded by the general practitioner. **RESULTS:** 9 of 96 (9%) children with a diagnosis of autism (cases) and 41 of 449 (9%) children without autism (matched controls) had a history of gastrointestinal disorders before the index date (the date of first recorded diagnosis of autism in the cases and the same date for controls). The estimated odds ratio for a history of gastrointestinal disorders among children with autism compared with children without autism was 1.0 (95% confidence interval 0.5 to 2.2). **CONCLUSIONS:** No evidence was found that children with autism were more likely than children without autism to have had defined gastrointestinal disorders at any time before their diagnosis of autism.

3.2.26. Fillano, J.J., Goldenthal, M.J., Rhodes, C.H., Marin-Garcia, J. "Mitochondrial dysfunction in patients with hypotonia, epilepsy, autism, and developmental delay: HEADD syndrome." *J Child Neurol* 2002 Jun;17(6):435-9.

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A group of 12 children clinically presenting with hypotonia, intractable epilepsy, autism, and developmental delay, who did not fall into previously described categories of mitochondrial encephalomyopathy, were evaluated for mitochondrial respiratory enzyme activity levels, mitochondrial DNA, and mitochondrial structural abnormalities. Reduced levels in specific respiratory activities were found solely in enzymes with subunits encoded by mitochondrial DNA in seven of eight biopsied skeletal muscle specimens evaluated. Five cases exhibited increased levels of large-scale mitochondrial DNA deletions, whereas pathogenic point mutations previously described in association with mitochondrial encephalomyopathies were not found. Mitochondrial structural abnormalities were present in three of four patients examined. Our findings suggest that mitochondrial dysfunction, including extensive abnormalities in specific enzyme activities, mitochondrial structure, and mitochondrial DNA integrity, may be present in children with a clinical constellation including hypotonia, epileptic seizures, autism, and developmental delay. The acronym HEADD is presented here to facilitate pursuit of mitochondrial defects in patients with this clinical constellation after other causes have been excluded.

3.2.27. Finegold, S.M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M.L., Bolte, E., McTeague, M., Sandler, R., Wexler, H., Marlowe, E.M., Collins, M.D., Lawson, P.A., Summanen, P., Baysallar, M., Tomzynski, T.J., Read, E., Johnson, E., Rolfe, R., Nasir, P., Shah, H., Haake, D.A., Manning, P., Kaul, A. "Gastrointestinal microflora studies in late-onset autism." *Clin Infect Dis* 2002 Sep 1;35(Suppl 1):S6-S16.

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Some cases of late-onset (regressive) autism may involve abnormal flora because oral vancomycin, which is poorly absorbed, may lead to significant improvement in these children. Fecal flora of children with regressive autism was compared with that of control children, and clostridial counts were higher. The number of clostridial species found in the stools of children with autism was greater than in the stools of control children. Children with autism had 9 species of *Clostridium* not found in controls, whereas controls yielded only 3 species not found in children with autism. In all, there were 25 different clostridial species found. In gastric and duodenal specimens, the most striking finding was total absence of non-spore-forming anaerobes and microaerophilic bacteria from control children and significant numbers of such bacteria from children with autism. These studies demonstrate significant alterations in the upper and lower intestinal flora of children with late-onset autism and may provide insights into the nature of this disorder.

3.2.28. Dhossche, D., Applegate, H., Abraham, A., Maertens, P., Bland, L., Bencsath, A., Martinez, J. "Elevated plasma gamma-aminobutyric acid (GABA) levels in autistic youngsters: stimulus for a GABA hypothesis of autism." *Med Sci Monit* 2002 Aug;8(8):PR1-6.

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BACKGROUND: Autistic Disorder is an early-onset developmental disorder with severe lifelong impact on social functioning, communication, and behavior. There is currently no marker or cure. The pathophysiology and etiology are obscure. Evidence for abnormal gamma-aminobutyric acid (GABA) function in Autistic Disorders is limited. A few case-reports and small studies have reported differences in GABA levels in plasma, platelets, and urine, compared to controls. Further studies on abnormalities of GABA function in Autistic Disorder are warranted. **MATERIAL/METHODS:** Plasma GABA levels were measured using a new and sensitive technique, based on gas chromatography/mass spectrometry, in a small group of youngsters with Autistic Disorder and Attention-Deficit/Hyperactivity Disorder. Participants were outpatients between ages 5-15, satisfying modern criteria for these disorders. **RESULTS:** Elevated plasma GABA levels were found in youngsters with Autistic Disorder. Psychotropic medications did not seem to affect plasma GABA levels in this study. Plasma GABA levels decreased with age. **CONCLUSIONS:** Elevated plasma GABA levels may be a biochemical marker of Autistic Disorder. This study supports the hypothesis that GABAergic mechanisms play a role in

the etiology or pathophysiology of Autistic Disorder. However, the hypothesis remains unspecified owing to lack of research. Future studies on the clinical associations of seizure disorders, mood disorders, and catatonia in autistic people may provide the necessary data to formulate a coherent theory of GABA dysfunction in Autistic Disorder. More trials of medication with known or suspected effects on GABA function are warranted.

3.2.29. Vojdani, A., Campbell, A.W., Anyanwu, E., Kashanian, A., Bock, K., Vojdani, E. "Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, *Chlamydia pneumoniae* and *Streptococcus group A*." *J Neuroimmunol* 2002 Aug;129(1-2):168-77.

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We measured autoantibodies against nine different neuron-specific antigens and three cross-reactive peptides in the sera of autistic subjects and healthy controls by means of enzyme-linked immunosorbent assay (ELISA) testing. The antigens were myelin basic protein (MBP), myelin-associated glycoprotein (MAG), ganglioside (GM1), sulfatide (SULF), chondroitin sulfate (CONSO4), myelin oligodendrocyte glycoprotein (MOG), alpha,beta-crystallin (alpha,beta-CRYS), neurofilament proteins (NAFP), tubulin and three cross-reactive peptides, *Chlamydia pneumoniae* (CPP), streptococcal M protein (STM6P) and milk butyrophilin (BTN). Autistic children showed the highest levels of IgG, IgM and IgA antibodies against all neurologic antigens as well as the three cross-reactive peptides. These antibodies are specific because immune absorption demonstrated that only neuron-specific antigens or their cross-reactive epitopes could significantly reduce antibody levels. These antibodies may have been synthesized as a result of an alteration in the blood-brain barrier. This barrier promotes access of preexisting T-cells and central nervous system antigens to immunocompetent cells, which may start a vicious cycle. These results suggest a mechanism by which bacterial infections and milk antigens may modulate autoimmune responses in autism.

3.2.30. Rojas, D.C., Bawn, S.D., Benkers, T.L., Reite, M.L., Rogers, S.J. "Smaller left hemisphere planum temporale in adults with autistic disorder." *Neurosci Lett* 2002 Aug 16;328(3):237-40.

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The structure of the planum temporale is often disturbed in disorders with associated communication problems, particularly in auditory and language processing areas in the brain. We hypothesized that people with autism would have reduced left hemisphere volumes in the planum temporale, a language related brain structure. We performed magnetic resonance imaging scans of 15 adults with autistic disorder

and 15 comparison subjects, and measured the volume of gray matter in the planum temporale and Heschl's gyrus (HG) in both hemispheres. Planum temporale volume reduced in the left hemisphere of the autism group ($P < 0.003$). No differences in HG volumes were observed between the two groups. The volume reduction seen in the left hemisphere of the autism group may suggest an early neurodevelopmental disturbance in autism that impacts language development.

3.2.31. Singh, V.K., Lin, S.X., Newell, E., Nelson, C. "Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism." *J Biomed Sci* 2002 Jul-Aug;9(4):359-64.

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Autoimmunity to the central nervous system (CNS), especially to myelin basic protein (MBP), may play a causal role in autism, a neurodevelopmental disorder. Because many autistic children harbor elevated levels of measles antibodies, we conducted a serological study of measles-mumps-rubella (MMR) and MBP autoantibodies. Using serum samples of 125 autistic children and 92 control children, antibodies were assayed by ELISA or immunoblotting methods. ELISA analysis showed a significant increase in the level of MMR antibodies in autistic children. Immunoblotting analysis revealed the presence of an unusual MMR antibody in 75 of 125 (60%) autistic sera but not in control sera. This antibody specifically detected a protein of 73-75 kD of MMR. This protein band, as analyzed with monoclonal antibodies, was immunopositive for measles hemagglutinin (HA) protein but not for measles nucleoprotein and rubella or mumps viral proteins. Thus the MMR antibody in autistic sera detected measles HA protein, which is unique to the measles subunit of the vaccine. Furthermore, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and CNS autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of autism. Copyright 2002 National Science Council, ROC and S. Karger AG, Basel

3.2.32. Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., Dager, S.R. "Brain structural abnormalities in young children with autism spectrum disorder." *Neurology* 2002 Jul 23;59(2):184-92.

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OBJECTIVE: To explore the specific gross neuroanatomic substrates of this brain developmental disorder, the authors examine brain morphometric features in a large sample of carefully diagnosed 3- to 4-year-old children with autism spectrum disorder (ASD) compared with age-matched control groups of typically developing (TD) children and developmentally delayed (DD) children. **METHODS:** Volumes of the cerebrum, cerebellum, amygdala, and hippocampus

were measured from three-dimensional coronal MR images acquired from 45 children with ASD, 26 TD children, and 14 DD children. The volumes were analyzed with respect to age, sex, volume of the cerebrum, and clinical status. **RESULTS:** Children with ASD were found to have significantly increased cerebral volumes compared with TD and DD children. Cerebellar volume for the ASD group was increased in comparison with the TD group, but this increase was proportional to overall increases in cerebral volume. The DD group had smaller cerebellar volumes compared with both of the other groups. Measurements of amygdalae and hippocampi in this group of young children with ASD revealed enlargement bilaterally that was proportional to overall increases in total cerebral volume. There were similar findings of cerebral enlargement for both girls and boys with ASD. For subregion analyses, structural abnormalities were observed primarily in boys, although this may reflect low statistical power issues because of the small sample (seven girls with ASD) studied. Among the ASD group, structural findings were independent of nonverbal IQ. In a subgroup of children with ASD with strictly defined autism, amygdalar enlargement was in excess of increased cerebral volume. **CONCLUSIONS:** These structural findings suggest abnormal brain developmental processes early in the clinical course of autism. Research currently is underway to better elucidate mechanisms underlying these structural abnormalities and their longitudinal progression.

3.2.33. Aylward, E.H., Minshew, N.J., Field, K., Sparks, B.F., Singh, N. "Effects of age on brain volume and head circumference in autism." *Neurology* 2002 Jul 23;59(2):175-83.

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OBJECTIVE: To determine whether brain volume, as assessed on MRI scans, differs between individuals with autism and control subjects, and whether such differences are affected by age. **BACKGROUND:** Previous studies have found increased brain weight, head circumference, and MRI brain volume in children with autism. However, studies of brain size in adults with autism have yielded conflicting results. The authors hypothesize that enlargement of the brain may be a feature of brain development during early childhood in autism that normalizes with maturational processes. **METHODS:** The authors measured total brain volumes from 1.5-mm coronal MRI scans in 67 non-mentally retarded children and adults with autism and 83 healthy community volunteers, ranging in age from 8 to 46 years. Head circumference was also measured. Groups did not differ on age, sex, verbal IQ, or socioeconomic status. **RESULTS:** Brain volumes were significantly larger for children with autism 12 years old and younger compared with normally developing children, when controlling for height. Brain volumes for individuals older than age 12 did not differ between the autism and control groups. Head circumference was increased in both younger and older groups of subjects with autism, suggesting that those subjects older than age 12 had increased brain

volumes as children. **CONCLUSIONS:** Brain development in autism follows an abnormal pattern, with accelerated growth in early life that results in brain enlargement in childhood. Brain volume in adolescents and adults with autism is, however, normal, and appears to be due to a slight decrease in brain volume for these individuals at the same time that normal children are experiencing a slight increase.

3.2.34. Sokol, D.K., Dunn, D.W., Edwards-Brown, M., Feinberg, J. "Hydrogen proton magnetic resonance spectroscopy in autism: preliminary evidence of elevated choline/creatine ratio." *J Child Neurol* 2002 Apr;17(4):245-9.

Department of Neurology, Indiana University School of Medicine, Indianapolis, USA. dksokol@iupui.edu

Hydrogen proton magnetic resonance spectroscopy is only beginning to be studied in autistic individuals. We report an association between hydrogen proton magnetic resonance spectroscopy choline/creatine ratios and severity of autism as measured by the Children's Autistic Rating Scale (Pearson $r = .657$, $P = .04$) in 10 autistic children. Hydrogen proton magnetic resonance spectroscopy choline/creatine ratio measures the concentration of cytosolic choline including free choline used in the synthesis of acetylcholine. Elevation in this ratio has been interpreted as a result of membrane degradation such as caused by a tumor or, alternatively, as a result of choline synthesis associated with increased cellular proliferation. Recent neuropathologic evidence has implicated disruption of acetylcholine transmission in the brains of autistic adults. A case-controlled study of hydrogen proton magnetic resonance spectroscopy choline/creatine ratios is warranted.

3.2.35. Mouridsen, S.E., Rich, B., Isager, T. "Body mass index in male and female children with infantile autism." *Autism* 2002 Jun;6(2):197-205.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

Morphometry, the measurement of forms, is an ancient practice. Recently, evidence has grown to support the notion that aberrant neurodevelopment may play a role in the pathophysiology of autism. Is the body, like the brain, affected by abnormal development in these patients? The aim of this study was to evaluate body mass index (BMI) of children with infantile autism, by comparing the BMI of 117 children with infantile autism with the corresponding BMI percentiles in an age- and sex-matched reference population. The BMI distribution of the male, but not female, children with infantile autism was significantly lower than that of the age-matched reference population. There was no evidence that BMI was associated with intelligence or socioeconomic status among children with infantile autism.

3.2.36. Kim, S.J., Young, L.J., Gonen, D., Veenstra-VanderWeele, J., Courchesne, R., Courchesne, E., Lord, C., Leventhal, B.L., Cook, E.H.Jr., Insel, T.R. "Transmission disequilibrium testing of arginine vasopressin receptor 1A (AVPR1A) polymorphisms in autism." *Mol Psychiatry* 2002;7(5):503-7.

Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry, University of Chicago, IL 60637, USA.

Impairment in social reciprocity is a central component of autism. In preclinical studies, arginine vasopressin (AVP) has been shown to increase a range of social behaviors, including affiliation and attachment, via the V(1a) receptor (AVPR1A) in the brain. Both the behavioral effects of AVP and the neural distribution of the V1a receptor vary greatly across mammalian species. This difference in regional receptor expression as well as differences in social behavior may result from a highly variable repetitive sequence in the 5' flanking region of the V1a gene (AVPR1A). Given this comparative evidence for a role in inter-species variation in social behavior, we explored whether within our own species, variation in the human AVPR1A may contribute to individual variations in social behavior, with autism representing an extreme form of social impairment. We genotyped two microsatellite polymorphisms from the 5' flanking region of AVPR1A for 115 autism trios and found nominally significant transmission disequilibrium between autism and one of the microsatellite markers by Multiallelic Transmission/Disequilibrium test (MTDT) that was not significant after Bonferroni correction. We also screened approximately 2 kb of the 5' flanking region and the coding region and identified 10 single nucleotide polymorphisms.

3.2.37. Lee, M., Martin-Ruiz, C., Graham, A., Court, J., Jaros, E., Perry, R., Iversen, P., Bauman, M., Perry, E. "Nicotinic receptor abnormalities in the cerebellar cortex in autism." *Brain* 2002 Jul;125(Pt 7):1483-95.

MRC/University of Newcastle Upon Tyne Development in Clinical Brain Ageing, Newcastle upon Tyne, UK.

Autism is a common developmental disorder associated with structural and inferred neurochemical abnormalities of the brain. Cerebellar abnormalities frequently have been identified, based on neuroimaging or neuropathology. Recently, the cholinergic neurotransmitter system has been implicated on the basis of nicotinic receptor loss in the cerebral cortex. Cerebellar cholinergic activities were therefore investigated in autopsy tissue from a series of autistic individuals. The presynaptic cholinergic enzyme, choline acetyltransferase, together with nicotinic and muscarinic receptor subtypes were compared in the cerebellum from age-matched mentally retarded autistic (eight), normal control (10) and non-autistic mentally retarded individuals (11). The nicotinic receptor binding the agonist epibatidine (the high affinity receptor subtype, consisting primarily of alpha3 and alpha4, together with beta2 receptor subunits) was significantly reduced by 40-50% in the granule cell, Purkinje and molecular layers in the autistic compared with the normal group ($P < 0.05$). There was an opposite increase (3-fold) in the nicotinic receptor binding alpha-bungarotoxin (to the alpha7 subunit) which reached significance in the granule cell layer ($P < 0.05$). These receptor changes were paralleled by a significant reduction ($P < 0.05$) and non-significant increase, respectively, of alpha4 and alpha7 receptor subunit

immunoreactivity measured using western blotting. Immunohistochemically loss of alpha(4) reactivity was apparent from Purkinje and the other cell layers, with increased alpha7 reactivity in the granule cell layer. There were no significant changes in choline acetyltransferase activity, or in muscarinic M1 and M2 receptor subtypes in autism. In the non-autistic mentally retarded group, the only significant abnormality was a reduction in epibatidine binding in the granule cell and Purkinje layers. In two autistic cases examined histologically, Purkinje cell loss was observed in multiple lobules throughout the vermis and hemispheres. This was more severe in one case with epilepsy, which also showed vermis folial malformation. The case with less severe Purkinje cell loss also showed cerebellar white matter thinning and demyelination. These findings indicate a loss of the cerebellar nicotinic alpha4 receptor subunit in autism which may relate to the loss of Purkinje cells, and a compensatory increase in the alpha7 subunit. It remains to be determined how these receptor abnormalities are involved in neurodevelopment in autism and what is the relationship to mental function. Since nicotinic receptor agonists enhance attentional function and also induce an elevation in the high affinity receptor, nicotinic therapy in autism may be worth considering.

3.2.38. Christensen, K., Mortensen, P.B. "Facial clefting and psychiatric diseases: a follow-up of the Danish 1936-1987 Facial Cleft cohort." *Cleft Palate Craniofac J* 2002 Jul;39(4):392-6.

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OBJECTIVE: This study assesses whether patients with facial cleft have an increased risk of psychiatric diseases. **DESIGN:** Through the Danish Facial Cleft Database, patients with facial cleft born between 1936 and 1987 in Denmark were identified, and the admission pattern for these patients with facial cleft was available for the period 1969 through 1993 through the Danish Psychiatric Central Registry. **PARTICIPANTS:** A total of 6,462 patients with facial cleft followed up for a total of 127,068 person-years. **MAIN OUTCOME MEASURES** Hospitalization for psychiatric diseases. The expected number of admissions for the cleft population was calculated by multiplication of the observed person-years with admission rates for Denmark stratified for sex, 1-year age group, and 1-year calendar period. **RESULTS:** A total of 284 patients with facial cleft (4.4%) were hospitalized for psychiatric diseases. The relative risk of hospitalization was 1.65 (95% confidence interval 1.3 to 2.0) for patients with isolated cleft palate (CP) and 1.15 (95% confidence interval 0.99 to 1.29) for patients with cleft lip +/- cleft palate (CL(P)). The overall risk estimates were above unity for both CP and CL(P) in all major diagnosis groups, neurosis and autism (for CL(P)) being the only exceptions. The excess risk was not accounted for by patients with known associated anomalies/syndromes. **CONCLUSION:** The risk of hospitalized mental disorders in general is increased in patients with CP but not to any substantial degree in patients with CL(P). Both groups had an increased risk of mental retardation and substance abuse,

but the risk for schizophrenia or bipolar illness was not statistically significantly increased, compared with the background population. Further, our data provide no evidence that the psychosocial stressors associated with CL(P) and its treatment have any substantial impact on the risk for hospitalized mental illness.

3.2.39. Lazar, N.A., Luna, B., Sweeney, J.A., Eddy, W.F. "Combining brains: a survey of methods for statistical pooling of information." *Neuroimage* 2002 Jun;16(2):538-50.

Department of Statistics, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, USA.

More than one subject is scanned in a typical functional brain imaging experiment. How can the scientist make best use of the acquired data to map the specific areas of the brain that become active during the performance of different tasks? It is clear that we can gain both scientific and statistical power by pooling the images from multiple subjects; furthermore, for the comparison of groups of subjects (clinical patients vs healthy controls, children of different ages, left-handed people vs right-handed people, as just some examples), it is essential to have a "group map" to represent each population and to form the basis of a statistical test. While the importance of combining images for these purposes has been recognized, there has not been an organized attempt on the part of neuroscientists to understand the different statistical approaches to this problem, which have various strengths and weaknesses. In this paper we review some popular methods for combining information, and demonstrate the surveyed techniques on a sample data set. Given a combination of brain images, the researcher needs to interpret the result and decide on areas of activation; the question of thresholding is critical here and is also explored. 2002 Elsevier Science (USA)

3.2.40. Skoyles, J.R. "Is autism due to cerebral-cerebellum disconnection?" *Med Hypotheses* 2002 Apr;58(4):332-6.

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Autism has been linked to thalidomide exposure at 20-24 days gestation. At this stage, the embryo is roughly the size of this 'C', and has yet to develop its brain (except for brainstem cranial motor nerve nuclei). The neuropathology responsible for autism is presently unknown, but whatever it is, it must logically be one that can be induced by such an early occurring brainstem cranial motor nerve nuclei defect. Many mental faculties impaired in autism (such as theory of mind) depend upon the prefrontal cortex. The maturation of cerebral-cerebellar connections, due to oddities in axon development, is vulnerable to pre-existing brainstem nuclei integrity. Many higher cognitions (including prefrontal ones) are dependent upon these links raising the possibility that abnormalities in them might produce autism. I conjecture that impaired cerebral-cerebellar connections, whether caused early, as by thalidomide, or later (including postnatally) by other factors, is the missing neuropathological cause of autism. Copyright 2002 Elsevier Science Ltd. All rights reserved.

3.2.41. Horvath, K., Perman, J.A. "Autism and gastrointestinal symptoms." *Curr Gastroenterol Rep* 2002 Jun;4(3):251-8. Publication Types: Review, Review, Tutorial.

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Autism is a collection of behavioral symptoms characterized by dysfunction in social interaction and communication in affected children. It is typically associated with restrictive, repetitive, and stereotypic behavior and manifests within the first 3 years of life. The cause of this disorder is not known. Over the past decade, a significant upswing in research has occurred to examine the biologic basis of autism. Recent clinical studies have revealed a high prevalence of gastrointestinal symptoms, inflammation, and dysfunction in children with autism. Mild to moderate degrees of inflammation were found in both the upper and lower intestinal tract. In addition, decreased sulfation capacity of the liver, pathologic intestinal permeability, increased secretory response to intravenous secretin injection, and decreased digestive enzyme activities were reported in many children with autism. Treatment of digestive problems appears to have positive effects on autistic behavior. These new observations represent only a piece of the unsolved autism "puzzle" and should stimulate more research into the brain-gut connection.

3.2.42. Stromland, K., Sjogreen, L., Miller, M., Gillberg, C., Wentz, E., Johansson, M., Nylen, O., Danielsson, A., Jacobsson, C., Andersson, J., Fernell, E. "Mobius sequence—a Swedish multidiscipline study." *Eur J Paediatr Neurol* 2002;6(1):35-45.

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Mobius sequence/syndrome is a rare disorder characterized by congenital palsy of the 6th and 7th cranial nerves. Other cranial nerves may be affected, skeletal and orofacial anomalies and mental retardation occur. The aims were to determine the frequency of associated clinical characteristics and to identify any pregnancy or environmental factors in patients with Mobius sequence. A prospective study of 25 Swedes with apparent involvement of the 6th and 7th cranial nerves was performed and 25 patients, 1 month to 55 years old, were examined. Obvious associated systemic anomalies observed included: limb malformations (10), Poland anomaly (2), hypodontia (7), microglossia (6), cleft palate (4), hearing impairment (5) and external ear malformation (1). Pronounced functional abnormalities were observed involving facial expression (16), speech (13), eating and swallowing (12) and difficulty in sucking in infancy (11). Six patients had an autistic syndrome, one an autistic-like condition, and mental retardation was found in all these patients. No common aetiological cause was found but their mothers' pregnancy histories revealed a history of benzodiazepines (1), bleeding during pregnancy (8), spontaneous abortion (7) and chorion villus sampling in the second month of pregnancy (1). In conclusion, many patients had multiple problems with eating

and communication resulting from facial palsy, cleft palate and tongue anomalies. Autism and mental retardation was diagnosed in one-third of the patients. Awareness of the wide spectrum of manifestations in Mobius sequence will assist in identification of the associated malformations and functional problems that are often seen and result in better care of the children.

3.2.43. Uhlmann, V., Martin, C.M., Sheils, O., Pilkington, L., Silva, I., Killalea, A., Murch, S.B., Walker-Smith, J., Thomson, M., Wakefield, A.J., O'Leary, J.J. "Potential viral pathogenic mechanism for new variant inflammatory bowel disease." *Mol Pathol* 2002 Apr;55(2):84-90.

Department of Pathology, Coombe Women's Hospital, Dublin 8, Ireland.

AIMS: A new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia) has been described in a cohort of children with developmental disorder. This study investigates the presence of persistent measles virus in the intestinal tissue of these patients (new variant inflammatory bowel disease) and a series of controls by molecular analysis. **METHODS:** Formalin fixed, paraffin wax embedded and fresh frozen biopsies from the terminal ileum were examined from affected children and histological normal controls. The measles virus Fusion (F) and Haemagglutinin (H) genes were detected by TaqMan reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in situ PCR. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody. **RESULTS:** Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300,00 copies/ng total RNA. **CONCLUSIONS:** The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

3.2.44. Wakefield, A.J., Puleston, J.M., Montgomery, S.M., Anthony, A., O'Leary, J.J., Murch, S.H. "Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands." *Aliment Pharmacol Ther* 2002 Apr;16(4):663-74. Publication Types: Review, Review, Tutorial.

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There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic

encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

3.2.45. Bolte, S., Ozkara, N., Poustka, F. "Autism spectrum disorders and low body weight: is there really a systematic association?" *Int J Eat Disord* 2002 Apr;31(3):349-51.

Department of Child and Adolescent Psychiatry, University of Frankfurt, Frankfurt, Germany.

OBJECTIVE: To examine the relationship between autism spectrum disorders and low body weight. **METHOD:** The effect of maladaptive social and communicative behavior as well as stereotyped features on the normative body mass index (BMI) was analyzed in 103 subjects with autism or Asperger syndrome. Statistics were controlled for medication, neurological signs, overactivity, and general intelligence. **RESULTS:** Twenty-eight percent of the male individuals had a BMI in the fifth percentile or below. Except for hyperactive behavior, none of the predictors showed a significant association with BMI. None of the subjects met diagnostic criteria for anorexia nervosa. **DISCUSSION:** Although low body weight is often present in male subjects with autism or Asperger syndrome, results indicate that this link is inconsistent and partly mediated by hyperactivity. The co-occurrence of autism spectrum disorders and anorexia nervosa is probably due to chance. Copyright 2002 by Wiley Periodicals, Inc.

3.2.46. Taylor, B., Miller, E., Lingam, R., Andrews, N., Simmons, A., Stowe, J. "Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study." *BMJ* 2002 Feb 16;324(7334):393-6.

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Objectives: To investigate whether measles, mumps, and rubella (MMR) vaccination is associated with bowel problems and developmental regression in children with autism, looking for evidence of a "new variant" form of autism. Design:

Population study with case note review linked to independently recorded vaccine data. Setting: Five health districts in north east London. Participants: 278 children with core autism and 195 with atypical autism, mainly identified from computerised disability registers and born between 1979 and 1998. Main outcome measures: Recorded bowel problems lasting at least three months, age of reported regression of the child's development where it was a feature, and relation of these to MMR vaccination. Results: The proportion of children with developmental regression (25% overall) or bowel symptoms (17%) did not change significantly (P value for trend 0.50 and 0.47, respectively) during the 20 years from 1979, a period which included the introduction of MMR vaccination in October 1988. No significant difference was found in rates of bowel problems or regression in children who received the MMR vaccine before their parents became concerned about their development (where MMR might have caused or triggered the autism with regression or bowel problem), compared with those who received it only after such concern and those who had not received the MMR vaccine. A possible association between non-specific bowel problems and regression in children with autism was seen but this was unrelated to MMR vaccination. Conclusions: These findings provide no support for an MMR associated "new variant" form of autism with developmental regression and bowel problems, and further evidence against involvement of MMR vaccine in the initiation of autism.

3.2.47. Croonenberghs, J., Bosmans, F., Deboutte, D., Kenis, G., Maes, M. "Activation of the inflammatory response system in autism." *Neuropsychobiology* 2002;45(1):1-6.

University Centre of Child and Adolescent Psychiatry, Antwerp, Belgium.

BACKGROUND/ AIM : There is now some evidence that autism may be accompanied by abnormalities in the inflammatory response system (IRS). Products of the IRS, such as inflammatory cytokines, may induce some of the behavioral symptoms of autism, such as social withdrawal, resistance to novelty and sleep disturbances. The main aim of the present study was to examine whether autism is accompanied by an activation of the IRS. METHODS: We measured the production of interleukin (IL) -6, IL-10, the IL-1 receptor antagonist (IL -IRA), interferon (IFN) - gamma and tumor necrosis factor (TNF) -alpha by whole blood and the serum concentrations of IL-6, the IL-2 receptor (IL-2R) and IL-IRA. RESULTS: This study showed a significantly increased production of IFN-gamma and IL-IRA and a trend toward a significantly increased production of IL-6 and TNF-alpha by whole blood of autistic children. There were no significant differences in the serum concentrations of IL -6, IL-2R and IL-IRA between autistic and normal children. CONCLUSIONS: These results suggest that autism may be accompanied by an activation of the monocytic (increased IL-IRA) and Th-1-like (increased IFN - gamma) arm of the IRS. It is hypothesized that increased production of proinflammatory cytokines could play a role in the pathophysiology of autism. Copyright 2002. karger AG, Basel

3.2.48. Binstock, T. "Anterior insular cortex: linking intestinal pathology and brain function in autism-spectrum subgroups." *Med Hypotheses* 2001 Dec;57(6):714-7. Publication Types: Review, Review, Tutorial.

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Autism includes deficits in communications skills and is associated with intestinal pathology. Numerous parents and some physicians report that an autistic child's attention and language improve in response to treatments which eliminate certain dietary antigens and/or which improve intestinal health. For at least some autism-spectrum children, the link between intestinal pathology, attention, and language may derive from shared neuroanatomic pathways within the anterior insular cortex (aIC); from a neurotrophic virus such as herpes simplex (HSV) migrating within afferents to the insular cortex; and/or from synaptic exhaustion in the aIC as induced by chronically inappropriate neuronal activity in the enteric nervous system and/or its vagal efferents.

3.2.49. Junaid, M.A., Pullarkat, R.K. "Proteomic approach for the elucidation of biological defects in autism." *J Autism Dev Disord* 2001 Dec;31(6):557-60.

Department of Developmental Biochemistry, New York State Institute for Basic Research in Developmental Disabilities, Staten Island 10314, USA.

Proteomic-based approaches, which examine expressed proteins in tissues or cells, have great potential in the elucidation of biological defects in heterogeneous neurodevelopmental disorders such as autism. In this approach, tissue or cellular proteins from control and affected subjects are separated on two-dimensional (2-D) polyacrylamide gel electrophoresis, and those proteins that show marked changes in the concentration between control and affected subjects are identified by mass spectroscopy. This method has been successfully applied in the elucidation of the molecular biological defect in classic late-infantile neuronal ceroid lipofuscinosis (Sleat et al., 1997). Unlike the classical methods of genome-wide screening for chromosomal localization followed by positional cloning, the proteomic approach requires limited number of tissue samples and the study can be completed in a relatively short time. Currently, these methods are available for relatively abundant proteins and generally are not applicable for hydrophobic proteins because 2-D gel electrophoresis is not very effective in the analysis of hydrophobic proteins. The genetic defect results in either total loss of proteins or changes in molecular weight and/or isoelectric point will be detectable by the proteomic method. Because autism is a neurogenetic disorder, brain is the tissue of choice for proteomic study. For an oligogenic disorder such as autism, at least some of the aberrant (genes) proteins may be identified by this technology.

3.2.50. Pickett, J. "Current investigations in autism brain tissue research." *J Autism Dev Disord* 2001 Dec;31(6):521-7.

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Brain tissue research has developed into a high-tech, multifaceted approach to understanding neurological disorders. Directed toward autism spectrum disorders, this investigative approach combines with other disciplines, such as imaging and genetics, to help explain the range and intensity of behaviors that characterize these disorders. This report is intended as an update on current autism brain research efforts and has a dual purpose: first, to disseminate information to the scientific community in the hope of stimulating more thinking about autism research and future collaborations; and second, to let the autism community know what is happening with this precious resource that was donated in the hope of determining the cause of autism and finding effective treatments.

3.2.51. Kohyama, J., Ohinata, J., Hasegawa, T. "Disturbance of phasic chin muscle activity during rapid-eye-movement sleep." *Brain Dev* 2001 Dec; 23 Suppl 1: S104-7. Publication Types: Review, Review, Tutorial.

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In patients with Rett syndrome (RS), a peculiar type of disturbance in phasic chin muscle activity during rapid-eye-movement sleep (REMS) (e.g. and elevation of phasic inhibition index (PII) without and affection of tonic inhibition index (TII)) has been reported. The similar disturbance in REMS was reported not only in child patients with infantile spasms, severe myoclonic epilepsy in infancy (SMEI), severe nocturnal enuresis, and autism but also in adult patients with Parkinson's disease (PD). Except for SMEI and PD, patients with the other four clinical entities including RS could express autistic tendency. Since the responsible lesion for the occurrence of and elevation of PII with a normal TII value is likely to be in the pontine tegmentum, this subcortical structure is hypothesized to be involved in the appearance of autistic tendency.

3.2.52. Purcell, A.E., Jeon, O.H., Zimmerman, A.W., Blue, M.E., Pevsner, J. "Postmortem brain abnormalities of the glutamate neurotransmitter system in autism." *Neurology* 2001 Nov 13;57(9): 1618-28.

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BACKGROUND: Studies examining the brains of individuals with autism have identified anatomic and pathologic changes in regions such as the cerebellum and hippocampus. Little, if anything, is known, however, about the molecules that are involved in the pathogenesis of this disorder. **OBJECTIVE:** To identify genes with abnormal expression levels in the cerebella of subjects with autism. **METHOD:** Brain samples from a total of 10 individuals with autism and 23 matched controls were collected, mainly from the cerebellum. Two cDNA microarray technologies were used to identify genes that were significantly up- or downregulated in autism. The abnormal mRNA or protein levels of several genes identified by microarray analysis were investigated using PCR with reverse

transcription and Western blotting alpha-Amino-3-hydroxy-5-methyl-4- were examined with receptor autoradiography in the cerebellum, caudate-putamen, and prefrontal cortex. **RESULTS:** The mRNA levels of several genes were significantly increased in autism, including excitatory amino acid transporter 1 and glutamate receptor AMPA 1, two members of the glutamate system. Abnormalities in the protein or mRNA levels of several additional molecules in the glutamate system were identified on further analysis, including glutamate receptor binding proteins. AMPA - type glutamate receptor density was decreased in the cerebellum of individuals with autism ($p < 0.005$). **CONCLUSIONS:** Subjects with autism may have specific abnormalities in the AMPA-type glutamate receptors and glutamate transporters in the cerebellum. These abnormalities may be directly involved in the pathogenesis of the disorder.

3.2.53. Hashimoto, T., Sasaki, M., Sugai, K., Hanaoka, S., Fukumizu, M., Kato, T. "Paroxysmal discharges on EEG in young autistic patients are frequent in frontal regions." *J Med Invest* 2001 Aug; 48(3-4): 175-80.

Department of Education for Handicapped Children, Naruto University of Education, 748 Nakashima, Takashima, Naruto-cho, Naruto-city, Tokushima 772-8502, Japan.

EEGs were recorded in 86 autistic patients during sleep. Epileptic discharges were observed in 37 cases (43%). Twenty-seven (73%) of these 37 cases had localized spikes, 8 had multiple spike foci, one had generalized spikes, and one had both multiple spike foci and generalized spikes. Forty-seven epileptic discharge foci were registered in 36 cases, the exception being one with generalized spikes. Thirty-six (76.6%) of the registered 47 epileptic discharge foci were in the frontal region, one (2.1%) in the temporal region, 7 (14.1%) in the centro-parietal region, and 3 (6.4%) in the occipital region. Twenty (55.6%) of the 36 frontal spikes were at midline (11 at Fz and 9 at Cz), 8 on the left side, and 8 on the right side. The dipole of midline spikes was in the deep midline frontal region. These results suggest that frontal dysfunctions are important in the mechanism of symptoms in autism.

3.2.54. Jyonouchi, H., Sun, S., Le, H. "Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression." *J Neuroimmunol* 2001 Nov 1; 120(1-2): 170-9.

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We determined innate and adaptive immune responses in children with developmental regression and autism spectrum disorders (ASD, N=71), developmentally normal siblings (N=23) and controls (N=17). With lipopolysaccharide (LPS), a stimulate for innate immunity, peripheral blood mononuclear cells (PBMCs) from 59/71 (83.1%) ASD patients produced >2 SD above the control mean (CM) values of TNF-alpha, IL-1beta, and/or IL-6 produced by control PBMCs. ASD PBMCs produced higher levels of proinflammatory/counter-

regulatory cytokines without stimuli than controls. With stimulants of phytohemagglutinin (PHA), tetanus, IL-12p70, and IL-18, PBMCs from 47.9% to 60% of ASD patients produced >2SD above the CM values of TNF-alpha depending on stimulants. Our results indicate excessive innate immune responses in a number of ASD children that may be most evident in TNF-alpha production.

3.2.55. Vancassel, S., Durand, G., Barthelemy, C., Lejeune, B., Martineau, J., Guilloteau, D., Andres, C., Chalon, S. "Plasma fatty acid levels in autistic children." *Prostaglandins Leukot Essent Fatty Acids* 2001 Jul;65(1):1-7

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Phospholipid fatty acids are major structural components of neuronal cell membranes, which modulate membrane fluidity and hence function. Evidence from clinical and biochemical sources have indicated changes in the metabolism of fatty acids in several psychiatric disorders. We examined the phospholipid fatty acids in the plasma of a population of autistic subjects compared to mentally retarded controls. Our results showed a marked reduction in the levels of 22:6n-3 (23%) in the autistic subjects, resulting in significantly lower levels of total (n-3) polyunsaturated fatty acids (PUFA) (20%), without significant reduction in the (n-6) PUFA series, and consequently a significant increase in the (n-6)/(n-3) ratio (25%). These variations are discussed in terms of potential differences in PUFA dietary intake, metabolism, or incorporation into cellular membranes between the two groups of subjects. These results open up interesting perspectives for the investigation of new biological indices in autism. Moreover, this might have new therapeutic implications in terms of child nutrition. Copyright 2001 Harcourt Publishers Ltd.

3.2.56. Hayashi, E. "Seasonal changes in sleep and behavioral problems in a pubescent case with autism." *Psychiatry Clin Neurosci* 2001 Jun;55(3):223-4.

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This study reports on the seasonal changes in sleep problems and behavioral problems in a pubescent case with autism. His care diary, kept for 1 year, showed seasonal changes of sleep and behavioral problems, and that his behavioral problems preceded his sleep problems.

3.2.57. Hardan, A.Y., Minshew, N.J., Mallikarjunn, M., Keshavan, M.S. "Brain volume in autism." *J Child Neurol* 2001 Jun;16(6):421-4.

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Increased brain size has been observed in individuals with autism with a wide range of cognitive functioning. The purpose of this investigation was to obtain measurements of the brain volume in a sample of nonmentally retarded autistic

individuals. Magnetic resonance imaging scans from 16 nonmentally retarded individuals with autism and 19 male volunteer comparison subjects were obtained and the following structures were measured: third, fourth, and lateral ventricles and intracranial and cerebral volumes. Mean cerebral and third ventricle volumes in the autistic subjects were significantly greater than in the controls when adjusted for intracranial volume. No other significant results were found. Our finding of increased brain volume in autism is consistent with previous reports in the literature. Additional longitudinal neuroimaging and, more importantly, neuropathologic studies are warranted to provide a better understanding of the complexities underlying increased brain size in autism.

3.2.58. Johnson, S. "Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease?" *Med Hypotheses* 2001 May;56(5):641-5. Moses Lake, Washington 98837, USA.

Zinc has several crucial functions in brain development and maintenance: it binds to p53, preventing it from binding to supercoiled DNA and ensuring that p53 cause the expression of several paramount genes, such as the one that encodes for the type I receptors to pituitary adenine cyclase-activator peptide (PACAP), which directs embryonic development of the brain cortex, adrenal glands, etc.; it is required for the production of CuZnSOD and Zn-thionein, which are essential to prevent oxidative damage; it is required for many proteins, some of them with Zn fingers, many of them essential enzymes for growth and homeostasis. For example, the synthesis of serotonin involves Zn enzymes and since serotonin is necessary for melatonin synthesis, a Zn deficiency may result in low levels of both hormones. Unfortunately, Zn levels tend to be low when there is excess Cu and Cd. Moreover, high estrogen levels tend to cause increased absorption of Cu and Cd, and smoking and eating food contaminated with Cd result in high levels of the latter. Furthermore, ethanol ingestion increases the elimination of Zn and Mg (which acts as a cofactor for CuZnSOD). Increased Cu levels may also be found in people with Wilson's disease, which is a rather rare disease. However, the heterozygote form (only one faulty copy of the chromosome) is not so rare. Therefore, the developing fetus of a pregnant women who is low in Zn and high in Cu may experience major difficulties in the early development of the brain, which may later manifest themselves as schizophrenia, autism or epilepsy. Similarly, a person who gradually accumulates Cu, will tend to experience a gradual depletion of Zn, with a corresponding increase in oxidative damage, eventually leading to Parkinson's disease. Also discussed are the crucial roles of histidine, histamine, vitamin D, essential fatty acids, vitamin E, peroxynitrate, etc. in the possible oxidative damage involved in these mental diseases. Copyright 2001 Harcourt Publishers Ltd.

3.2.59. Nelson, K.B., Grether, J.K., Croen, L.A., Dambrosia, J.M., Dickens, B.F., Jelliffe, L.L., Hansen, R.L., Phillips, T.M. "Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation." *Ann Neurol* 2001 May;49(5):597-606.

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There has been little exploration of major biologic regulators of cerebral development in autism. In archived neonatal blood of children with autistic spectrum disorders (n = 69), mental retardation without autism (n = 60), or cerebral palsy (CP, n = 63) and of control children (n = 54), we used recycling immunoaffinity chromatography to measure the neuropeptides substance P (SP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), calcitonin gene-related peptide (CGRP), and the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT4/5). Neonatal concentrations of VIP, CGRP, BDNF, and NT4/5 were higher (ANOVA, all p values < 0.0001 by Scheffe test for pairwise differences) in children in the autistic spectrum and in those with mental retardation without autism than in control children. In 99% of children with autism and 97% with mental retardation, levels of at least one of these substances exceeded those of all control children. Concentrations were similar in subgroups of the autistic spectrum (core syndrome with or without mental retardation, other autistic spectrum disorders with or without mental retardation) and in the presence or absence of a history of regression. Among children with mental retardation, concentrations did not differ by severity or known cause (n = 11, including 4 with Down syndrome). Concentrations of measured substances were similar in children with CP as compared with control subjects. SP, PACAP, NGF, and NT3 were not different by diagnostic group. No measured analyte distinguished children with autism from children with mental retardation alone. In autism and in a heterogeneous group of disorders of cognitive function, overexpression of certain neuropeptides and neurotrophins was observed in peripheral blood drawn in the first days of life.

3.2.60. Miles, J.H., Hadden, L.L., Takahashi, T.N., Hillman, R.E. "Head circumference is an independent clinical finding associated with autism." *Am J Med Genet* 2000 Dec 11;95(4):339-50.

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Occipitofrontal circumference (OFC) is one of the few physical findings in autism that varies significantly from the norm and is distinct and measurable. As part of a study of genetic heterogeneity of autism, we scrutinized data from a large sample of patients with idiopathic autism (N = 137), using OFC as the categorizing variable. The OFC standard deviation (OFCSD) values of the autistic probands (0.61+/-1.6) varied significantly from that of the normal population (0.0+/-1.0), (P<0.001). Comparison of the macrocephalic (OFCSD > 2.0, N = 32) with the normocephalic individuals (-2 SD < OFCSD < +2 SD, N = 95) showed no significant differences in sex ratio, morphological status, IQ, seizure prevalence, or recurrence risks. The macrocephalic individuals were slightly less apt than those with normocephaly to have a family history of

Attention Deficit Hyperactivity Disorder (ADHD) (P<0.05). Each clinical subgroup of autism probands, defined on the basis of phenotypic status, type of onset, seizure history, or IQ, had a higher than normal mean OFC indicating that macrocephaly is an independent clinical trait in autism. As in the non-autistic population, macrocephaly was highly familial with 45% of the macrocephalic and 37% of the normocephalic probands having at least one macrocephalic parent. Microcephaly, however, was an independent significant variable that predicted the presence of other phenotypic or genetic traits and outcome. The microcephalic patients were more likely to have abnormal physical morphology, structural brain malformations, lower IQ, and seizures. Their sex ratio was closer to normal, and their relatives had a higher incidence of seizures.

3.2.61. Dufke, A., Eggermann, K., Balg, S., Stengel-Rutkowski, S., Enders, H., Kaiser, P. "A second case of inv(4)pat with both recombinants in the offspring: rec dup(4q) in a girl with Wolf-Hirschhorn syndrome and rec dup(4p)." *Cytogenet Cell Genet* 2000;91(1-4):85-9.

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In a girl presenting with features of Wolf-Hirschhorn syndrome, cytogenetic and molecular cytogenetic analysis revealed a rearranged chromosome 4 with monosomy of the distal bands 4pter->4p16.2 and trisomy of the distal bands 4q35.1->4qter [rec dup(4q)] due to a large, paternal pericentric inversion. In the following two pregnancies, prenatal diagnosis showed the same imbalance in one fetus and a reverse segmental imbalance [rec dup(4p)] in the other. We discuss the recombination risk of the given inversion with respect to the size of the inverted segment and the viability of the recombinants. The high frequency of recombinants in this family and others suggests a high recurrence risk in similar cases with large pericentric inversions comprising almost entire chromosomes. Copyright 2001 S. Karger AG, Basel.

3.2.62. McClelland, J.L. "The basis of hyperspecificity in autism: a preliminary suggestion based on properties of neural nets." *J Autism Dev Disord* 2000 Oct;30(5):497-502.

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This article reviews a few key ideas about the representation of information in neural networks and uses these ideas to address one aspect of autism, namely, the apparent hyperspecificity that is often seen in autistic children's application of previously acquired information. Hyperspecificity is seen as reflecting a possible feature of the neural codes used to represent concepts in the autistic brain.

3.2.63. Szatmari, P. "The classification of autism, Asperger's syndrome, and pervasive developmental disorder." *Can J Psychiatry* 2000 Oct;45(8):731-8. Publication Types: Review, Review, Tutorial.

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OBJECTIVE: The current classification of the pervasive developmental disorders (PDDs) as conceptualized in both the DSM-IV and ICD-10 is deeply unsatisfying to many parents, front-line clinicians, and academic researchers. Is the diagnostic validity of the various disorders simply lacking empirical data for full substantiation, or does the overall conceptualization of the category have more fundamental problems, not reflecting the "true" nature of the phenomena? This paper argues the latter hypothesis. I review the historical development of the classification of PDD, summarize recent empirical data on issues of reliability and validity, and suggest a new approach to classification and understanding.

3.2.64. Marazziti, D., Muratori, F., Cesari, A., Masala, I., Baroni, S., Giannaccini, G., Dell'Osso, L., Cosenza, A., Pfanner, P., Cassano, G.B. "Increased density of the platelet serotonin transporter in autism." *Pharmacopsychiatry* 2000 Sep;33(5):165-8. Publication Types: Clinical Trial.

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BACKGROUND: Various data have shown the involvement of serotonin (5-HT) in autism. The presence of the 5-HT transporter in platelets, similar to the same structure located in presynaptic serotonergic neurons, has produced a series of studies aimed at assessing its functionality in this disorder, but the ensuing findings are quite controversial. For this reason, we investigated the 5-HT transporter by means of the specific binding of [3H]-Paroxetine ([3H]-Par), which is currently considered the first-choice ligand for labeling it, in platelets of 20 autistic children and adolescents, as compared with healthy control subjects. **METHODS:** Twenty children and adolescents of both sexes suffering from autism according to DSM IV criteria were included in the study and compared with a similar group of healthy control subjects. Platelet membranes and the binding of [3H]-Par were carried out according to standardized protocols. **RESULTS:** The results showed a significantly higher density of [3H]-Par binding sites in autistic children than in healthy control subjects. **CONCLUSIONS:** These findings support the presence of a serotonergic dysfunction in autism and would suggest that the 5-HT transporter may have a specific role in this disorder, also in the light of its recently proposed role in brain development.

3.2.65. Hardan, A.Y., Minshew, N.J., Keshavan, M.S. "Corpus callosum size in autism." *Neurology* 2000 Oct 10;55(7):1033-6.

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The size of the seven subregions of the corpus callosum was measured on MRI scans from 22 non-mentally retarded autistic subjects and 22 individually matched controls. Areas

of the anterior subregions were smaller in the autistic group. In a subsample, measurements were adjusted for intracranial, total brain, and white matter volumes and the differences between groups remained significant. No differences were found in the other subregions. This observation is consistent with the frontal lobe dysfunction reported in autism.

3.2.66. Wakefield, A.J., Anthony, A., Murch, S.H., Thomson, M., Montgomery, S.M., Davies, S., O'Leary, J.J., Berelowitz, M., Walker-Smith, J.A. "Enterocolitis in children with developmental disorders." *Am J Gastroenterol* 2000 Sep;95(9):2285-95.

University Department of Medicine, Royal Free and University College Medical School, London, United Kingdom.

OBJECTIVE: Intestinal pathology, i.e., ileocolonic lymphoid nodular hyperplasia (LNH) and mucosal inflammation, has been described in children with developmental disorders. This study describes some of the endoscopic and pathological characteristics in a group of children with developmental disorders (affected children) that are associated with behavioral regression and bowel symptoms, and compares them with pediatric controls. **METHODS:** Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 yr, range 3-16; 53 male). Developmental diagnoses were autism (50 patients), Asperger's syndrome (five), disintegrative disorder (two), attention deficit hyperactivity disorder (ADHD) (one), schizophrenia (one), and dyslexia (one). Severity of ileal LNH was graded (0-3) in both affected children and 37 developmentally normal controls (median age 11 yr, range 2-13 yr) who were investigated for possible inflammatory bowel disease (IBD). Tissue sections were reviewed by three pathologists and scored on a standard proforma. Data were compared with ileocolonic biopsies from 22 histologically normal children (controls) and 20 children with ulcerative colitis (UC), scored in an identical manner. Gut pathogens were sought routinely. **RESULTS:** Ileal LNH was present in 54 of 58 (93%) affected children and in five of 35 (14.3%) controls ($p < 0.001$). Colonic LNH was present in 18 of 60 (30%) affected children and in two of 37 (5.4%) controls ($p < 0.01$). Histologically, reactive follicular hyperplasia was present in 46 of 52 (88.5%) ileal biopsies from affected children and in four of 14 (29%) with UC, but not in non-IBD controls ($p < 0.01$). Active ileitis was present in four of 51 (8%) affected children but not in controls. Chronic colitis was identified in 53 of 60 (88%) affected children compared with one of 22 (4.5%) controls and in 20 of 20 (100%) with UC. Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls ($p < 0.001$). **CONCLUSIONS:** A new variant of inflammatory bowel disease is present in this group of children with developmental disorders.

3.2.67. Ringman, J.M., Jankovic, J. "Occurrence of tics in Asperger's syndrome and autistic disorder." *J Child Neurol* 2000 Jun;15(6):394-400.

Department of Neurology, University of California, Irvine School of Medicine, USA.

Asperger's syndrome is a condition in the autistic spectrum in which language development is normal. Patients with Asperger's syndrome frequently exhibit repetitive movements (stereotypies), and can have motor and phonic tics in addition to other behavioral abnormalities. We present 12 patients with autistic spectrum disorders who were referred to our Movement Disorders Clinic for evaluation of tics. Eight of the 12 had normal language development and therefore met criteria for Asperger's syndrome. All patients exhibited stereotypic movements; in addition, seven had tics and six of these met diagnostic criteria for Tourette syndrome. Of the six patients with clinical features of both Asperger's syndrome and Tourette syndrome, three had severe congenital sensory deficits. The autistic patients in our series were clinically heterogeneous and though tics were clearly present, other aberrant movements demonstrated by them were harder to classify. Our series confirms the wide range of clinical manifestations in Asperger's syndrome and autism, including tics and other features of Tourette syndrome. Furthermore, it suggests that sensory deprivation contributes to the development of adventitious movements in this population.

3.2.68. Schreck, K.A., Mulick, J.A. "Parental report of sleep problems in children with autism." *J Autism Dev Disord* 2000 Apr;30(2):127-35.

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This research evaluated parent reports of sleep behaviors of four groups of children: those with Autism or Pervasive Developmental Disorders, those with General Mental Retardation alone, those attending Special Education classes (with no MR diagnosis), and a control group of similar aged children without a developmental diagnosis. Diagnostic classification and demographic information were determined through parent report, report of classroom registration, and the Gilliam Autism Rating Scale (Gilliam, 1995). To evaluate sleeping behavior the study used a 28-item, five-factor scale (Behavioral Evaluation of Disorders of Sleep/BEDS; Schreck, 1997/1998) constructed from the diagnostic criteria for childhood sleep disorders found in the International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD, American Sleep Disorders Association, 1990). Findings suggest that reports of parents with children with autistic characteristics exhibit expected quantities of sleep, but parent perception of their sleep difficulties and sleep quality is different for children with autism than for children in all other study groups.

3.2.69. Wing, L., Shah, A. "Catatonia in autistic spectrum disorders." *Br J Psychiatry* 2000 Apr;176:357-62.

Centre for Social and Communication Disorders, Bromley, Kent.

BACKGROUND: The clinical pictures of autistic spectrum disorders include features described in catatonia. **AIMS:** To examine the severe exacerbation of the catatonic features of autistic disorders in adolescence or early adult life, which occurs in some individuals. **METHOD:** A semi-structured

interview schedule was used to collect information from parents or other care-givers concerning 506 referrals to a specialist clinic for autistic spectrum disorders. Individuals with severe exacerbation of catatonic features were compared with a same-age group of referrals without this type of deterioration in skills and behaviour. **RESULTS:** Seventeen per cent of referrals aged 15 or over had severe exacerbation of catatonic features. They were significantly more likely than the comparison group to have had, before the onset of the change in behaviour, impaired language and passivity in social interaction. **CONCLUSIONS:** Catatonia is a later complication of autistic spectrum disorders, which adds considerably to the burden of caring. More research is needed to identify causes, neuropathology, and early signs of vulnerability.

3.2.70. Berney, T.P. "Autism—an evolving concept." *Br J Psychiatry* 2000 Jan;176:20-5. Publication Types: Review, Review Literature.

Northgate and Prudhoe NHS Trust, Prudhoe Hospital, Northumberland.

BACKGROUND: The rapid increase in research endeavour has not kept pace with the advent of well-publicized theories and treatments for autism. **AIMS:** To explore some of the newer developments in biological research into autism. **METHOD:** A review of recent publications and presentations. **RESULTS:** The concept is shifting from the narrow perception of aloof autism, described by Kanner, to a wider one that includes a spectrum extending to a broader, subclinical phenotype. The genetic basis has been established; now we need to discover the location and interaction of the relevant sites. There is considerable interest in the bowel as a pathogenetic agent, particularly in the effects of exogenous opioids and multiple viral infection (the latter posing a public health problem). Also of concern is the role of (potentially treatable) epilepsy, analogous to the Laudau-Kleffner syndrome. **CONCLUSIONS:** In the absence of a cure, the implementation of ideas will continue to outstrip factual evidence. Clinicians are challenged by the availability of information (and misinformation), particularly on the internet.

3.2.71. Carper, R.A., Courchesne, E. "Inverse correlation between frontal lobe and cerebellum sizes in children with autism." *Brain* 2000 Apr;123 (Pt 4):836-44.

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Certain cognitive and behavioural deficits suggest that the frontal lobe functions abnormally in patients with autism, but little anatomical research is available to either verify or refute this. In contrast, several neuropathological and neuroimaging studies have demonstrated anatomical abnormalities in the cerebellum in autistic patients. The current study shows that frontal lobe cortex volume is increased in a subset of patients with autism and that this increase correlates with the degree of cerebellar abnormality. This evidence of concurrent structural abnormalities in both the frontal lobe and the cerebellum has important implications for understanding the development and persistence of the autistic disorder.

3.2.72. Sabaratnam M. "Pathological and neuropathological findings in two males with fragile-X syndrome." *J Intellect Disabil Res* 2000 Feb;44 (Pt 1):81-5. Publication Types: Review, Review of Reported Cases.

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The present paper addresses post mortem pathological and neuropathological findings in two males with fragile-X syndrome, aged 67 and 87 years. Both subjects died from sudden, unexpected cardiovascular causes, and both showed abnormalities of the mitral valve, ventricular hypertrophy and cardiomegaly. Both cases demonstrated macrocephaly characteristic of the classical Martin-Bell phenotype in FRAXA. There was increased brain weight in both cases: macroscopically, both cerebral and cerebellar hemispheres appeared normal, but dilated lateral ventricles were seen; and microscopic examination of the brain in case 2 showed normal hexalaminar architecture and no gross neuronal dropout. The hippocampus showed mild CA4 pyramidal cell loss and associated gliosis. The cerebellum showed focal Purkinje cell loss and corresponding Bergmann gliosis. Whilst there is a need to delineate the microscopic features of fragile-X syndrome from those of the ageing process, there is an urgent need for more systematic neuropathological studies of fragile-X syndrome; the increased brain weight and Purkinje cell loss in autism and fragile-X syndrome reopens the debate on these two conditions. The case for further research into the cardiac anomalies in fragile-X syndrome is also strengthened by the findings. Finally, the present report confirms the role of interstitial cell hyperplasia as the major cause of megalotestes in this condition.

3.2.73. Beadle-Brown, J., Murphy, G., Wing, L., Gould, J., Shah, A., Holmes, N. "Changes in skills for people with intellectual disability: a follow-up of the Camberwell Cohort." *J Intellect Disabil Res* 2000 Feb;44 (Pt 1):12-24.

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The skills of a total population of children with severe intellectual disability and/or autism from Camberwell, South London, UK, and the initial follow-up data, taken when the subjects were adolescents and young adults (Shah 1986), are described in the present study. Changes in skills over time are presented within the categories of communication, self-care, and educational and cognitive skills, as assessed by the Handicaps, Behaviours and Skills schedule. The results indicated that skills had improved in many areas between times 1 and 2, but that this improvement was more noticeable for the children who had been youngest at time 1. The implications of these results and predictions for a further follow-up study are discussed.

3.2.74. Salerno, C., Siems, W.G., Crifo, C. "Succinylpurinemic autism: increased sensitivity of defective adenylosuccinate lyase towards 4-hydroxy-2-nonenal." *Biochim Biophys Acta* 2000 Mar 17;1500(3):335-41.

Department of Biochemical Sciences and Clinical Biochemistry Laboratory, University of Roma La Sapienza, I-00185, Rome, Italy.

We studied the effect of trans-4-hydroxy-2-nonenal on the wild-type human adenylosuccinate lyase and on the enzyme from a patient compound-heterozygous for two missense mutations (P75A/D397Y; McKusick 103050.0003/103050.0004). Both the enzymes were inhibited by 10-50 microM trans-4-hydroxy-2-nonenal in a concentration-dependent manner by means of a mixed-type co-operative mechanism. A significantly stronger inhibition was noticed in the presence of the defective enzyme. Nonanal and trans-2,3-nonenal inhibited the enzymes to a less extent and at about 10-times higher concentrations. Hydroxylamine reversed the inhibition by trans-4-hydroxy-2-nonenal, trans-2,3-nonenal or nonanal in the case of the wild-type enzyme, but it was ineffective to reverse the inhibition by trans-4-hydroxy-2-nonenal on the defective enzyme. Dithiothreitol slightly decreased the inhibition exerted by trans-4-hydroxy-2-nonenal on both the wild-type and the defective adenylosuccinate lyase, while it did not produce practically any change in the presence of trans-2,3-nonenal or nonanal.

3.2.75. Page, T., Coleman, M. "Purine metabolism abnormalities in a hyperuricosuric subclass of autism." *Biochim Biophys Acta* 2000 Mar 17;1500(3):291-6.

Department of Neurosciences, University of California, San Diego, School of Medicine, 9500 Gilman Drive, La Jolla, CA 92093-0624, USA.

A subclass of patients with classic infantile autism have uric acid excretion which is >2 S.D.s above the normal mean. These hyperuricosuric autistic individuals may comprise approx. 20% of the autistic population. In order to determine the metabolic basis for urate overexcretion in these patients, de novo purine synthesis was measured in the cultured skin fibroblasts of these patients by quantification of the radiolabeled purine compounds produced by incubation with radiolabeled sodium formate. For comparison, de novo purine synthesis in normal controls, in normouricosuric autistic patients, and cells from patients with other disorders in which excessive uric acid excretion is seen was also measured. These experiments showed that de novo purine synthesis is increased approx. 4-fold in the hyperuricosuric autistic patients. This increase was less than that found in other hyperuricosuric disorders. No unusual radiolabeled compounds (such as adenylosuccinate) were detected in these experiments, and no gross deficiencies of radiolabeled nucleotides were seen. However, the ratio of adenine to guanine nucleotides produced by de novo synthesis was found to be lower in the cells of the hyperuricosuric autistic patients than in the normal controls or the cells from patients with other disorders. These results indicate that the hyperuricosuric subclass of autistic patients have increased de novo purine synthesis, and that the increase is approximately that expected for the degree of urate overexcretion when compared to other hyperuricosuric disorders. No particular enzyme defect was suggested by either gross deficiency of a radiolabeled compound or the appearance of an unusual radiolabeled

compound, and no potentially neurotoxic metabolites were seen. Although an enzyme defect responsible for the accelerated purine synthesis was not identified, the abnormal ratio of adenine to guanine nucleotides suggests a defect in purine nucleotide interconversion.

3.2.76. Diomedì, M., Curatolo, P., Scalise, A., Placidi, F., Caretto, F., Gigli, G.L. "Sleep abnormalities in mentally retarded autistic subjects: Down's syndrome with mental retardation and normal subjects." *Brain Dev* 1999 Dec;21(8):548-53.

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We compared sleep parameters in mentally retarded infantile autism (MRIA) and mentally retarded Down's syndrome (MRDS) by means of polysomnography, evaluating traditional analysis with particular attention to the phasic components in each disorder. Data were compared with those obtained in normal subjects matched for age and sex. Mental age, Intellectual Quotient and the Childhood Autism Rating Scale were performed to obtain an estimation of the neuropsychological deficit. Abnormalities of phasic components of sleep and the presence of REM sleep components into non-REM sleep were observed in both MRIA and MRDS even if in different ways. In fact, MRDS subjects presented a reduction of REM sleep percentage and R index (number of high frequency REMs against number of low frequency REMs) and this was positively correlated to a low IQ. Unlike MRDS subjects, MRIA subjects did not show any parallelism between intellectual abilities and REM sleep deficit. In addition, the presence of undifferentiated sleep in autistic subjects implies a maturational deficit that is still present in adulthood. Finally, a high R index in MRIA was observed. This finding, which is not present in MRDS, could represent an estimation of the disorganized arrival of information caused by a dyscontrol or a reduction of inhibitor pathway. With reference to sleep mechanisms, our results suggest that the cognitive deficit in MRIA may differ from that of MRDS subjects. A maturational deficit of CNS with a dysfunction of brainstem monoaminergic neurons could represent the underlying mechanism.

3.2.77. Bruneau, N., Roux, S., Adrien, J.L., Barthelemy, C. "Auditory associative cortex dysfunction in children with autism: evidence from late auditory evoked potentials (N1 wave-T complex)." *Clin Neurophysiol* 1999 Nov;110(11):1927-34. Publication Types: Clinical Trial.

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OBJECTIVES: Auditory processing at the cortical level was investigated with late auditory evoked potentials (N1 wave-T complex) in 4-8-year-old autistic children with mental retardation and compared to both age-matched normal and mentally retarded children (16 children in each group). **METHODS:** Two negative peaks which occurred in the 80-200 ms latency range were analyzed according to stimulus

intensity level (50 to 80 dB SPL): the first culminated at fronto-central sites (N1b) and the second at bitemporal sites (N1c, equivalent to Tb of the T complex). The latter wave was the most prominent and reliable response in normal children at this age. **RESULTS:** Our results in autistic children indicated abnormalities of this wave with markedly smaller amplitude at bitemporal sites and pronounced peak latency delay (around 20 ms). Moreover, in both reference groups the intensity effect was found on both sides whereas in autistic children it was absent on the left side but present on the right. **CONCLUSION:** These findings in autistic children showing very disturbed verbal communication argue for dysfunction in brain areas involved in N1c generation i.e., the auditory associative cortex in the lateral part of the superior temporal gyrus, with more specific left side defects when auditory stimulus have to be processed.

3.2.78. Horvath, K., Papadimitriou, J.C., Rabszty, A., Drachenberg, C., Tildon, J.I. "Gastrointestinal abnormalities in children with autistic disorder." *J Pediatr* 1999 Nov;135(5):559-63.

Department of Pediatrics, University of Maryland School of Medicine, Baltimore, USA.

OBJECTIVES: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. **STUDY DESIGN:** Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. **RESULTS:** Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea. **CONCLUSIONS:** Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder.

3.2.79. Ghaziuddin, M., Zaccagnini, J., Tsai, L., Flardo, S. "Is megalencephaly specific to autism?" *J Intellect Disabil Res* 1999 Aug;43 (Pt 4):279-82.

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Several recent reports have described the presence of increased head circumference (megalencephaly) in patients with autism. Although some studies have described reports of megalencephaly in other disorders such as schizophrenia in adults, few such studies have been performed in children and adolescents. In the present study, the authors compared 20 subjects with autism/ pervasive developmental disorder (DSM-IV; all males; mean age = 10.9 years) with 20 controls with attention deficit hyperactivity disorder (DSM-IV; all males; mean age = 11.1 years). Four subjects and five controls had evidence of megalencephaly. In addition to their core symptoms, the autistic subjects with megalencephaly were hyperactive and impulsive. These findings suggest that megalencephaly may not be specific to autism, and when present, it may index the presence of additional symptoms such as hyperactivity and impulsivity.

3.2.80. Otsuka, H., Harada, M., Mori, K., Hisaoka, S., Nishitani, H. "Brain metabolites in the hippocampus-amygdala region and cerebellum in autism: an 1H-MR spectroscopy study." *Neuroradiology* 1999 Jul;41(7):517-9.

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Histological abnormalities of the brain in autism have been investigated extensively. We studied metabolites in the hippocampus-amygdala (HA) region and cerebellum. We examined the right HA region and left cerebellar hemisphere of 27 autistic patients 2-18 years old, 21 boys and 6 girls and 10 normal children 6-14 years old, 4 boys and 6 girls, using the STEAM sequence. This sequence was used to minimise the influence of relaxation times. The N-acetyl aspartate (NAA) concentration was significantly lower ($P = 0.042$) in autistic patients than in normal children (9.37 and 10.95 mM, respectively). There was no significant difference in other metabolites. The correlation coefficient (r value) of NAA between the HA region and cerebellum was 0.616. The decreased NAA concentration may be due to neuronal hypofunction or immature neurons. The NAA concentration in the HA region and cerebellum may be related, because of neuronal circuits or networks.

3.2.81. Chugani, D.C., Sundram, B.S., Behen, M., Lee, M.L., Moore, G.J. "Evidence of altered energy metabolism in autistic children." *Prog Neuropsychopharmacol Biol Psychiatry* 1999 May;23(4):635-41.

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1. In this pilot study, the authors investigated the hypotheses there are increased concentrations of lactate in brain and plasma and reduced brain concentrations of N-acetyl-aspartate (NAA) in autistic children. 2. NAA and lactate levels in the frontal lobe, temporal lobe and the cerebellum of 9 autistic children were compared to 5 sibling controls using MRS. Plasma lactate levels were measured in 15 autistic

children compared to 15 children with epilepsy. 3. Preliminary results show lower levels of NAA cerebellum in autistic children ($p = 0.043$). Lactate was detected in the frontal lobe in one autistic boy, but was not detected any of the other autistic subjects or siblings. 4. Plasma lactate levels were higher in the 15 autistic children compared to 15 children with epilepsy ($p = 0.0003$). 5. Higher plasma lactate in the autistic group is consistent with metabolic changes in some autistic children. The findings of altered brain NAA and lactate in autistic children suggest that MRS may be useful characterizing regional neurochemical and metabolic abnormalities in autistic children.

3.2.82. Levitt, J.G., Blanton, R., Capetillo-Cunliffe, L., Guthrie, D., Toga, A., McCracken, J.T. "Cerebellar vermis lobules VIII-X in autism." *Prog Neuropsychopharmacol Biol Psychiatry* 1999 May;23(4):625-33.

Department of Psychiatry, UCLA Neuropsychiatric Institute, USA.

1. The aim was to investigate cerebellar vermis cross-sectional area in a group of high-functioning autistic children and normal control children. 2. Cerebellar vermis area measurements were completed on MRI scans from 8 autistic children (mean age 12.5 +/- 2.2, mean IQ 83.3 +/- 11.9) and 21 normal children (mean age 12.0 +/- 2.8, mean IQ 115 +/- 11). 3. The area of cerebellar vermis lobules VIII-X was significantly smaller in the autistic children than in the normal control subjects. ANCOVA demonstrated a confounding effect of IQ on these results. 4. Larger studies of autistic and normal subjects will be needed to assess the relationship between cerebellar abnormalities, autistic symptoms and IQ.

3.2.83. Fombonne, E., Roge, B., Claverie, J., Courty, S., Fremolle, J. "Microcephaly and macrocephaly in autism." *J Autism Dev Disord* 1999 Apr;29(2):113-9. Publication Types: Clinical Trial.

Institute of Psychiatry, MRC Child Psychiatry Unit, London, United Kingdom.

Data from a series of 126 autistic children ages 2-16 years and referred to an Autism Diagnosis Unit in South-West France were examined. Macrocephaly (head circumference > 97th centile) was observed in 16.7% of the sample, a significantly higher proportion than that expected. Macrocephaly was more frequent among older subjects but was otherwise not associated with gender, developmental level, the presence of epilepsy or of medical disorders, or severity of autistic symptomatology. Microcephaly (head circumference < 3rd centile) was also significantly raised and found in 15.1% of the sample. Microcephaly was significantly associated with the presence of medical disorders. Results support those from recent studies suggesting a raised rate of macrocephaly in autism which, pooling published data, can be estimated to be 20%. It is argued that the raised incidence of microcephaly among low-functioning autistic subjects with medical disorders might have contributed to delay the recognition of an increased head circumference among a minority of subjects with idiopathic autism.

3.2.84. Leontovich, T.A., Mukhina, J.K., Fedorov, A.A., Belichenko, P.V. "Morphological study of the entorhinal cortex, hippocampal formation, and basal ganglia in Rett syndrome patients." *Neurobiol Dis* 1999 Apr;6(2):77-91.

Laboratory of Neuronal Structure, Russian Academy of Medical Sciences, Moscow, Russia.

Entorhinal cortex (EC), fascia dentata (FD), hippocampus (HP), and basal ganglia (BG) were studied in Rett syndrome (RS) cases and compared with control brains and an autism case. Kluver-Barrera and Golgi methods were used. In RS most of the areas of EC, HP, and FD showed severe cell hypochromia. In the EC all cells of layer II and most in layer III were in a state of total chromatolysis or were "ghost" cells, but the cells of layers V and VI were preserved and moderately hyperchromic. In FD and HP the majority of the granular cells and cells of CA3 and CA4 fields were severely hypochromic, whereas in the CA1 field most cells were normal or slightly hypercaryochromic. In BG mostly mild or moderate aberration from normal cell structure was observed: in striatum, mild hypercaryochromia of small neurons and more expressive hyperchromia of large neurons were found; and in pallidum, mild or moderate hypercaryochromia to severe hyperchromia in pallidum internum was found. Degeneration of thick myelinated fibers was evident in pallidum. Large striatal and pallidal neurons showed signs of constructive changes in Golgi slices. These data allow the determination of the cause of the main symptoms of RS. The motor disorders, including specific stereotyped movements, could be related to the enhanced activity of BG cells due to their deafferentation from the side of the neocortex and to supposed hyperactivity of the EC-striatal pathway; the mental retardation and epileptic seizures could be due to FD-HP involvement.

3.2.85. Harris, N.S., Courchesne, E., Townsend, J., Carper, R.A., Lord, C. "Neuroanatomic contributions to slowed orienting of attention in children with autism." *Brain Res Cogn Brain Res* 1999 May;8(1):61-71.

Laboratory for Research on the Neuroscience of Autism, Children's Hospital Research Center, La Jolla, San Diego, CA 92037, USA.

Previous research has demonstrated that adult autistic patients are abnormally slow to orient attention, with degree of slowed orienting associated with severity of cerebellar hypoplasia. This research was extended to children who, at ages two through six, met diagnostic criteria for autism and underwent magnetic resonance imaging (MRI). An average of 3 years later, when old enough to participate in behavioral experiments, the children returned to the laboratory and completed a spatial attention paradigm. Degree of slowed attentional orienting to visual cues was significantly correlated with degree of cerebellar hypoplasia, but not with size of other neuroanatomic regions. Additionally, there was a trend for orienting speed to differ between diagnostic outcome subgroups; children with confirmed diagnoses of autism at time of behavioral testing had larger orienting deficits than those who no longer met diagnostic criteria for autism. This

research is among the first to establish a specific brain-behavior link in autistic children. Copyright 1999 Elsevier Science B.V.

3.2.86. Courchesne, E., Muller, R.A., Saitoh, O. "Brain weight in autism: normal in the majority of cases, megalencephalic in rare cases." *Neurology* 1999 Mar 23;52(5):1057-9.

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The brain weights of 21 postmortem autism cases (5 new and 16 previously published) were compared with normal brain weights from six autopsy studies. Of the 21 cases, 17 had normal brain weights and 1 was micrencephalic. Compared with the normal median (1,460 g), three autism cases were megalencephalic: two (1,810 g and 1,820 g) had been previously reported and one (1,880 g) was a new case. Brain weight is thus normal in most postmortem cases of autism. There are, however, rare cases of megalencephaly and possibly micrencephaly.

3.2.87. Minshew, N.J., Luna, B., Sweeney, J.A. "Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism." *Neurology* 1999 Mar 23;52(5):917-22.

Department of Psychiatry, University of Pittsburgh School of Medicine, PA 15213, USA.

OBJECTIVE: To investigate the functional integrity of cerebellar and frontal systems in autism using oculomotor paradigms. **BACKGROUND:** Cerebellar and neocortical systems models of autism have been proposed. Courchesne and colleagues have argued that cognitive deficits such as shifting attention disturbances result from dysfunction of vermal lobules VI and VII. Such a vermal deficit should be associated with dysmetric saccadic eye movements because of the major role these areas play in guiding the motor precision of saccades. In contrast, neocortical models of autism predict intact saccade metrics, but impairments on tasks requiring the higher cognitive control of saccades. **METHODS:** A total of 26 rigorously diagnosed nonmentally retarded autistic subjects and 26 matched healthy control subjects were assessed with a visually guided saccade task and two volitional saccade tasks, the oculomotor delayed-response task and the antisaccade task. **RESULTS:** Metrics and dynamics of the visually guided saccades were normal in autistic subjects, documenting the absence of disturbances in cerebellar vermal lobules VI and VII and in automatic shifts of visual attention. Deficits were demonstrated on both volitional saccade tasks, indicating dysfunction in the circuitry of prefrontal cortex and its connections with the parietal cortex, and associated cognitive impairments in spatial working memory and in the ability to voluntarily suppress context-inappropriate responses. **CONCLUSIONS:** These findings demonstrate intrinsic neocortical, not cerebellar, dysfunction in autism, and parallel deficits in higher order cognitive mechanisms and not in elementary attentional and sensorimotor systems in autism.

3.2.88. Chugani, D.C., Muzik, O., Behen, M., Rothermel, R., Janisse, J.J., Lee, J., Chugani, H.T. "Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children." *Ann Neurol* 1999 Mar;45(3):287-95.

Department of Pediatrics, Children's Hospital of Michigan, Detroit 48201, USA.

Serotonin content, serotonin uptake sites, and serotonin receptor binding measured in animal studies are all higher in the developing brain, compared with adult values, and decline before puberty. Furthermore, a disruption of synaptic connectivity in sensory cortical regions can result from experimental increase or decrease of brain serotonin before puberty. The purpose of the present study was to determine whether brain serotonin synthesis capacity is higher in children than in adults and whether there are differences in serotonin synthesis capacity between autistic and nonautistic children. Serotonin synthesis capacity was measured in autistic and nonautistic children at different ages, using alpha[11C]methyl-L-tryptophan and positron emission tomography. Global brain values for serotonin synthesis capacity (K complex) were obtained for autistic children (n = 30), their nonautistic siblings (n = 8), and epileptic children without autism (n = 16). K-complex values were plotted according to age and fitted to linear and five-parameter functions, to determine developmental changes and differences in serotonin synthesis between groups. For

nonautistic children, serotonin synthesis capacity was more than 200% of adult values until the age of 5 years and then declined toward adult values. Serotonin synthesis capacity values declined at an earlier age in girls than in boys. In autistic children, serotonin synthesis capacity increased gradually between the ages of 2 years and 15 years to values 1.5 times adult normal values and showed no sex difference. Significant differences were detected between the autistic and epileptic groups and between the autistic and sibling groups for the change with age in the serotonin synthesis capacity. These data suggest that humans undergo a period of high brain serotonin synthesis capacity during childhood, and that this developmental process is disrupted in autistic children.

3.2.89. Sitholey, P., Aga, V.M., Agarwal, V., Prasad, M. "Childhood autism in tuberous sclerosis." *Indian J Pediatr* 1998 Jul-Aug;65(4):615-7.

Department of Psychiatry, K.G Medical College, Lucknow.

The article reports two cases of childhood autism in tuberous sclerosis (TS). Certain atypical features are highlighted. The probands did not show the common seizure types associated with either TS or autism. No ventricular dilatation, cerebral atrophy or temporal lobe involvement was evident. The high prevalence of childhood autism in TS probands with moderate to severe mental retardation has been emphasized.

MANIFESTATION

Social Issues

3.3.1. Verte, S., Roeyers, H., Buysse, A. "Behavioural problems, social competence and self-concept in siblings of children with autism." *Child Care Health Dev.* 2003 May;29(3):193-205.

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INTRODUCTION: This study investigated the psychological adjustment of siblings of children with high-functioning autism (HFA) in comparison with siblings of normally developing children in the domain of behavioural problems, social competence and self-concept. **METHOD:** Twenty-nine siblings of children with HFA and 29 siblings of children without a disorder participated in the study. Standardized, written questionnaires were used. **RESULTS:** Siblings of children with HFA, especially brothers and sisters between 6 and 11 years old, had more behavioural problems than siblings of the control group. Sisters of children with HFA ascribed higher social competence to themselves. Sisters of children with HFA between 12 and 16 years old had a more positive self-concept. In both groups siblings with a more negative self-concept had less social skills and siblings with a more positive self-concept scored better in the social domain. Finally, in accordance with the control group, the perception of the siblings' social competence of parents of children with HFA broadly matched the perception siblings had of themselves. **DISCUSSION:** Overall, siblings of children with HFA are not more susceptible to adaptation problems than siblings of children without a disorder. Implications for practice and further research are discussed.

3.3.2. Hastings, R.P. "Brief report: Behavioral adjustment of siblings of children with autism." *J Autism Dev Disord.* 2003 Feb;33(1):99-104..

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Existing research studies have shown mixed results relating to the impact upon children of having a sibling with a disability. However, siblings of children with autism may be more at risk than siblings of children with other disabilities. In the present study, data were gathered on 22 siblings of children with autism. These children were rated by their mothers as having more behavior problems and fewer prosocial behaviors than a normative sample. Analysis of variables predicting sibling behavioral adjustment revealed that boys with siblings who have autism, and also those younger than their sibling with autism, engaged in fewer prosocial behaviors. Psychological adjustment of mothers (stress) and the child with autism (behavior problems) were not predictive of sibling behavioral adjustment.

3.3.3. Blair, R.J. "Facial expressions, their communicatory functions and neuro-cognitive substrates." *Philos Trans R Soc Lond B Biol Sci.* 2003 Mar 29;358(1431):561-72. Publication Types: Review, Review, Academic.

Unit on Affective Cognitive Neuroscience, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institute of Health, Department of Health and

Human Services, Bethesda, MD 20892-2670, USA, blairj@intra.nimh.nih.gov.

Human emotional expressions serve a crucial communicatory role allowing the rapid transmission of valence information from one individual to another. This paper will review the literature on the neural mechanisms necessary for this communication: both the mechanisms involved in the production of emotional expressions and those involved in the interpretation of the emotional expressions of others. Finally, reference to the neuro-psychiatric disorders of autism, psychopathy and acquired sociopathy will be made. In these conditions, the appropriate processing of emotional expressions is impaired. In autism, it is argued that the basic response to emotional expressions remains intact but that there is impaired ability to represent the referent of the individual displaying the emotion. In psychopathy, the response to fearful and sad expressions is attenuated and this interferes with socialization resulting in an individual who fails to learn to avoid actions that result in harm to others. In acquired sociopathy, the response to angry expressions in particular is attenuated resulting in reduced regulation of social behaviour.

3.3.4. Engstrom, L., Ekstrom, L., Emilsson, B. "Psychosocial functioning in a group of Swedish adults with Asperger syndrome or high-functioning autism." *Autism.* 2003 Mar;7(1):99-110.

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This study reports on psychosocial functioning in Swedish adults with Asperger syndrome (AS) or high-functioning autism (HFA). A systematically selected sample of patients and relatives was interviewed concerning their psychosocial situation. The majority was living independently. All persons but one were unemployed. None was married and none had children. Only a few had some kind of partner. Most persons needed a high level of public and/or private support. The overall adjustment was rated good in 12 percent, fair in 75 percent and poor in 12 percent. Adult persons with AS/HFA have extensive need for support from their families and/or society. This information is important in order to provide adequate interventions that are in accordance with the expressed needs of the individuals themselves.

3.3.5. Bauminger, N., Shulman, C. "The development and maintenance of friendship in high-functioning children with autism: maternal perceptions." *Autism.* 2003 Mar;7(1):81-97.

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The current study investigated mothers' perceptions of the development of friendship in high-functioning children with autism and in typically developing children. Fourteen mothers in each group (autism, typical) completed the Childhood Friendship Survey regarding their children's friendships. Main results indicated that both groups (autism and typical) tended to have same-gender and same-age friendships. However,

friendships of children with autism differ compared with typical children's friendships on number of friends, friendship duration, frequency of meetings, and type of activities. Half of the friendships in the autism group were mixed (friendship with a typically developing child). Mixed differed from non-mixed friendships in that mixed pairs met and played mostly at home, whereas non-mixed pairs met and played at school. Factors contributing to the development and formation of friendship in each group are discussed.

3.3.6. Palermo, M.I. "Preventing filicide in families with autistic children." *Int J Offender Ther Comp Criminol.* 2003 Feb;47(1):47-57.

Division of Autism and Developmental Disabilities, Associazione Anni Verdi, Centro Sperimentale per l'Autismo, Via Sbricoli 8, Rome, Italy 00148.

Autism is a complex neurodevelopmental disorder that affects social behaviors and parent-child interaction. It has been associated with an increased risk of social victimization, and a recent rise in number of acts of filicide of developmentally disabled children has included several cases of autism. In this article, possible risk factors for filicidal behavior in families with autistic children and prevention strategies are reviewed.

3.3.7. Gray, D.F. "Gender and coping: the parents of children with high functioning autism." *Soc Sci Med.* 2003 Feb;56(3):631-42.

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Gender is a concept that is frequently discussed in the literature on stress, coping and illness. Research has reported that women are more vulnerable than men are to stressful events and use different strategies to cope with them. Furthermore, it is often asserted that these gender-based differences in coping may partially explain the differential impact of stressful events on men and women. Unfortunately, much of this research has equated gender with sex and failed to contextualise the experience of illness and coping. This paper presents a qualitative analysis of the role of gender and coping among parents of children with high functioning autism or Asperger's syndrome in an Australian sample. It attempts to analyse the different meanings of the disability for mothers and fathers and describes the various strategies that parents use to cope with their child's disability.

3.3.8. Gilotty, L., Kenworthy, L., Sirian, L., Black, D.O., Wagner, A.E. "Adaptive skills and executive function in autism spectrum disorders." *Neuropsychol Dev Cogn Sect C Child Neuropsychol.* 2002 Dec;8(4):241-8.

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There is active debate regarding the nature of executive dysfunction in autism. Additionally, investigations have yet to show a relationship between deficits in executive function

and the everyday behavioral difficulties that may originate from them. The present study examined the relationship between executive abilities and adaptive behavior in 35 children with Autism Spectrum Disorders, using two parent reports of everyday functioning, the Vineland Adaptive Behavior Scales (VABS) and the Behavior Rating Inventory of Executive Function (BRIEF). Results found several relationships: The Initiate and Working Memory domains were negatively correlated with most domains of adaptive behavior. Also, the Communication and Socialization domains of the VABS were negatively correlated with several areas of executive functioning, suggesting that impairments in executive abilities are strongly associated with the deficits in communication, play and social relationships found in children with autism.

3.3.9. Elder, J.H., Valcante, G., Groce, S., Yarandi, H., Carlton, M.S. "Social interactions of children with autism in father-child and mother-child play sessions." *Pediatr Nurs.* 2002 Nov-Dec;28(6):573-8, 581.

University of Florida, College of Nursing, Gainesville, FL, USA.

Autism, or the broader category of autistic spectrum disorder (ASD), is a complex developmental disability characterized by qualitative impairments in social interaction and communication and restricted repetitive patterns of behavior. Specific aims of the investigation reported here were to (a) compare autistic child behaviors in clinic versus home settings, (b) compare father and mother behaviors in clinic versus home settings, and (c) characterize interactions of fathers with their autistic children and compare these with mother-child interactions. While results indicated that there were no statistically significant group differences between child behaviors in clinic versus home settings or in father versus mother behaviors, there was wide behavioral variability in each setting and differences when comparing individual cases. These findings are consistent with the clinical impression that autism is a syndrome with various symptom configurations and individual differences in behaviors.

3.3.10. Hillier, A., Allinson, L. "Understanding embarrassment among those with autism: breaking down the complex emotion of embarrassment among those with autism." *J Autism Dev Disord.* 2002 Dec;32(6):583-92.

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Scenarios manipulating various factors within the emotion of embarrassment, such as whether or not an audience was present when an embarrassing act was committed, the type of audience present, empathic embarrassment, etc., were presented to high-functioning participants with autism and comparison groups of those with learning difficulties and typically developing participants matched for verbal and nonverbal mental age. Participants were required to rate the level of embarrassment of the protagonist and justify their responses. It was predicted that those with autism would differ significantly from the comparison groups in their ratings

and also their ability to provide justifications. The results showed those with autism to have difficulty with such concepts as empathic embarrassment but showed a surprisingly good understanding of other variables manipulated such as the presence of an audience.

3.3.11. Beadle-Brown, J., Murphy, G., Wing, L., Gould, J., Shah, A., Holmes, N. **"Changes in social impairment for people with intellectual disabilities: a follow-up of the Camberwell cohort."** *J Autism Dev Disord* 2002 Jun;32(3):195-206.

Tizard Centre. University of Kent at Canterbury, UK.

The skills and social impairments of a total population of children with severe intellectual disabilities and/or autism from Camberwell, South London (Wing and Gould, 1978 and 1979), were assessed using the Handicaps, Behaviours and Skills schedule, and they were reassessed when they were adolescents and young adults (Shah, 1986). Changes in social impairment over time are presented here. As Shah (1986) had found with a smaller sample, social impairment remained relatively stable over time: on a simple "socially impaired" versus "sociable" dichotomous grouping, 93% did not change social group. Within the socially impaired group, there was a significant increase in impairment over time (i.e., people who were passive at Time 1, were aloof at Time 2). Implications of these results and predictions for a further follow-up study are discussed.

3.3.12. Carr, J.E., Dozier, C.L., Patel, M.R., Adams, A.N., Martin, N. **"Treatment of automatically reinforced object mouthing with noncontingent reinforcement and response blocking: experimental analysis and social validation."** *Res Dev Disabil* 2002 Jan-Feb;23(1):37-44. Publication Types: Evaluation Studies.

Department of Psychology, Western Michigan University, Kalamazoo 49008-5439, USA. jim.carr@wmich.edu

A brief functional analysis indicated the object mouthing of a young girl diagnosed with autism was maintained independent of social consequences. Separate and combined effects of response blocking and noncontingent reinforcement (with preferred stimuli) were then evaluated as treatments for object mouthing. Although both interventions were unsuccessful when implemented separately, combining them resulted in generalized reductions that were socially valid.

3.3.13. Kaminsky, L., Dewey, D. **"Psychosocial adjustment in siblings of children with autism."** *J Child Psychol Psychiatry* 2002 Feb;43(2):225-32.

University of Calgary, Alberta, Canada.

BACKGROUND: This study investigated psychosocial adjustment in siblings of children with autism compared to siblings of children with Down syndrome and siblings of normally developing children. In addition, the relationships between feelings of loneliness, social support and psychosocial adjustment, and the influence of gender and family size on psychological adjustment were examined. **METHODS:** Ninety

siblings (30 per group) between the ages of 8 and 18 and one parent of each child participated in this study. **RESULTS:** Results indicated that siblings of children with autism, as well as comparison siblings, were well adjusted and reported low levels of loneliness. Siblings of children with autism also reported that they received high levels of social support in their lives. **CONCLUSIONS:** Large family size appears to facilitate healthy adjustment in siblings of children with autism.

3.3.14. Hastings, R.P., Brown, T. **"Behavioural knowledge, causal beliefs and self-efficacy as predictors of special educators' emotional reactions to challenging behaviours."** *J Intellect Disabil Res* 2002 Feb;46(Pt 2):144-50.

Centre for Behavioural Research Analysis and Intervention in Developmental Disabilities, Department of Psychology, University of Southampton, Southampton, UK. rph@soton.ac.uk

Theoretical models and emerging empirical data suggest that the emotional reactions of staff to challenging behaviours may affect their responses to challenging behaviours and their psychological well-being. However, there have been few studies focusing on factors related to staff emotional reactions. Seventy staff working in educational environments with children with intellectual disability and/or autism completed a self-report questionnaire that measured demographic factors, behavioural causal beliefs, behavioural knowledge, perceived self-efficacy, and emotional reactions to challenging behaviours. Regression analyses revealed that behavioural causal beliefs were a positive predictor, and self-efficacy and behavioural knowledge were negative predictors of negative emotional reactions to challenging behaviours. Staff with formal qualifications also reported more negative emotional reactions. No other demographic factors emerged as significant predictors. The results suggest that behavioural causal beliefs, low self-efficacy and low behavioural knowledge may make staff vulnerable to experiencing negative emotional reactions to challenging behaviours. Researchers and clinicians need to address these issues in staff who work with people with challenging behaviours.

3.3.15. Schuntermann, P. **"Pervasive developmental disorder and parental adaptation: previewing and reviewing atypical development with parents in child psychiatric consultation."** *Harv Rev Psychiatry* 2002 Jan-Feb;10(1): 16-27.

Department of Psychiatry, Harvard Medical School, Children's Hospital, and Beth Israel Deaconess Medical Centre, Boston, MA, USA.

Parenting young children with pervasive developmental disorder engenders unique sustained stresses, which have been termed "burden of care" One specific source of stress for parents is the children's uneven developmental progress in which delays and accelerations of adaptive functioning may exist side by side. This paper proposes a clinical method that may be incorporated in to periodic child psychiatric consultations with parents of young children who have high-functioning autism or Asperger's disorder. Using a

semistructured technique, the clinician reviews with the parents the details of the child's recent developmental course and attempts to identify emergent skills that may serve to preview upcoming developmental issues and gains. This method is aimed at enhancing parental abilities to track and anticipate developmental progress and the resultant shifts in the parent-child relationship, in order to reduce one source of sustained parental stress. Case illustrations of children ages 2-8 years old are discussed in light of recent literature on adaptive issues in families of individuals with a chronic medical or psychiatric condition and, specifically, families of children with pervasive developmental disorder.

3.3.16. Spiker, D., Lotspeich, L.J., Dimiceli, S., Szatmari, P., Myers, R.M., Risch, N. "Birth order effects on nonverbal IQ scores in autism multiplex families." *J Autism Dev Disord* 2001 Oct;31(5): 449-60.

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, CA 94305-5719, USA.

Lord (1992) published a brief report showing a trend for decreasing nonverbal IQ scores with increasing birth order in a sample of 16 autism multiplex families, and urged replication in a larger sample. In this report, analysis of nonverbal IQ scores for a sample of 144 autism multiplex families indicated that non-verbal IQ scores were significantly lower in secondborn compared with firstborn siblings with autism. This birth order effect was independent of gender as well as the age differences within sib pairs. No such birth order effects were found for social or communicative deficits as measured by the Autism Diagnostic Interview- Revised

(ADI-R), but there was a modest tendency for increased scores for ritualistic behaviors for the firstborn sibs. Further, there were no gender differences on nonverbal IQ scores in this sample. Results are discussed in terms of Implications for genetic studies of autism.

3.3.17. Shu, B.C., Hsieh, H.C., Hsieh, S.C., Li, S.M. "Toward an understanding of mothering: the care giving process of mothers with autistic children." *J Nurs Res* 2001 Dec; 9(5):203-13.

Department of Nursing, National Cheng Kung University, Tainan, Taiwan, ROC.

The purpose of this study was to explore the care-giving experience of mothers with autistic children. In this qualitative study, a focus group and in-depth interviews were conducted with mothers with an autistic child to uncover the nature of their mothering experience. Data were analyzed for themes emerged: (a) the perception about their disabled child; (b) their special concerns for caring for this child and (c) reclaiming and discovering self through understanding the meaning of mothering. The results can help health workers to gain a deeper understanding of the care-giving process for mothers with an autistic child and facilitate mothers.

3.3.18. Olsson, M.B., Hwang, C.P. "Depression in mothers and fathers of children with intellectual disability." *J Intellect Disabil Res* 2001 Dec; 45 (Pt 6): 535-43.

University of Trollhattan - Uddevalla, Vanersborg, Sweden
Department of Psychology, Goteborg University, Goteborg, Sweden Malin.Broberg@1236.se

Parental depression was assessed using the Beck Depression Inventory (BDI) in 216 families with children with autism and / or intellectual disability (ID), and in 214 control families. Mothers with children with autism had higher depression scores (mean = 11.8) than mothers of children with ID without autism (mean = 9.2), who in turn, had higher depression scores than fathers of children with autism (mean = 6.2), fathers of children with ID without autism (mean = 5.0), and control mothers (mean = 5.0) and fathers (mean = 4.1). Forty-five percent of mothers with children with ID without autism and 50% of mothers with children with autism had elevated depression scores (BDI > 9), compared to 15-21% in the other groups. Single mothers of children with disabilities were found to be more vulnerable to severe depression than mothers living with a partner.

3.3.19. Jarbrink, K., Knapp, M. "The economic impact of autism in Britain." *Autism* 2001 Mar;5(1): 7-22. Publication Types: Meta-Analysis.

Institute of Psychiatry, London, UK.

Little is known about the economic impact of autism. This study estimated the economic consequences of autism in the United Kingdom, based on published evidence and on the reanalysis of data holdings at the Centre for the Economics of Mental Health (CEMH). With an assumed prevalence of 5 per 10,000, the annual societal cost for the UK was estimated to exceed 11 billion. The lifetime cost for a person with autism exceeded 12.4 million. The main costs were for living support and day activities. Family costs account for only 2.3 percent of the total cost, but a lack of relevant information limited our ability to estimate these costs. Minor improvements in life outcome for people with autism could substantially reduce costs over the lifetime.

3.3.20. McGregor, E., Campbell, E. "The attitudes of teachers in Scotland to the integration of Children with autism in to mainstream schools." *Autism* 2001 Jun;5(2): 189-207.

University of Dundee.

Around 4600 school-age children in Scotland fall within the spectrum of autistic disorders, of whom 780 have been identified in schools. This study sought the views of 23 specialist and 49 mainstream teachers, 22 with experience of autism, 27 without. They were questioned about the advantages and disadvantages of integration into mainstream for autistic children, their own ability to cope and predictors of success. Questionnaires were issued to special units and to mainstream primary and secondary schools. A minority of mainstream respondents believed children with autism should be integrated where possible. Mainstream teachers with experience of autism showed more confidence to deal with the children than those without experience. Many expressed concerns about effects on mainstream pupils but most were willing to undertake more training. Specialist teachers were

more positive, although they acknowledged possible disadvantages for both groups of children and stressed that the success of integration depends on the individual child.

3.3.21. Curran, A.L., Sharples, P.M., White, C., Knapp, M. "Time costs of caring for children with severe disabilities compared with caring for children without disabilities." *Dev Med Child Neurol* 2001 Aug;43(8):529-33.

Paediatric Neuroscience Unit, Institute of Child Health, University of Bristol, UK. Andrew.Curran@north-bristol.swest.nhs.uk

To assess time costs of caring for children with severe disabilities in the community compared to caring for children without disabilities, a diary- and questionnaire-based study was carried out. Sixteen complete data sets were obtained from families with children who have disabilities (mean age 8.7 years) and 31 complete data sets from families with normally developing children (mean age 4.9 years). Diagnoses in the study group included cerebral palsy, autism, Sanfillipo syndrome, lissencephaly, and osteogenesis imperfecta. Items of personal care per waking hour were significantly greater in children with disabilities than non-disabled children ($p < 0.001$). In the study group, there was no correlation ($r = -0.12$) between age and frequency of care whereas a significant correlation was observed between degree of disability as measured by the Functional Independence Measure for children (WeeFIM) and frequency of care items ($r = 0.89$). Twelve of the 16 mothers in the study group were not in paid employment. Twelve had little or no extended family support. Benefits awarded did not correlate with the degree of disability as measured by the WeeFIM ($r = -0.11$). Care needs of children with severe disabilities are significantly greater than those of non-disabled children and do not decrease with advancing age. Mothers of children with disabilities are unable to work outside the home because of these care needs. This brings the family income, even when benefits are included, to a level that is less than peer families with non-disabled children. A Functional Disability Score may help to achieve more appropriate allocation of state resources.

3.3.22. Swaim, K.F., Morgan, S.B. "Children's attitudes and behavioral intentions toward a peer with autistic behaviors: does a brief educational intervention have an effect?" *J Autism Dev Disord* 2001 Apr;31(2):195-205. Publication Types: Clinical Trial, Randomized Controlled Trial.

The University of Memphis, Tennessee 38152, USA.

This study examined children's ratings of attitudes and behavioral intentions toward a peer presented with or without autistic behaviors. The impact of information about autism on these ratings was investigated as well as age and gender effects. Third- and sixth-grade children ($N = 233$) were randomly assigned to view a video of the same boy in one of three conditions: No Autism, Autism, or Autism/Information. Children at both grade levels showed less positive attitudes toward the child in the two autism conditions. In rating their own behavioral intentions, children showed no differences between conditions. However, in attributing intentions to their

classmates, older children and girls gave lower ratings to the child in the autism conditions. Information about autism did not affect ratings of either attitudes or behavioral intentions as ascribed to self or others.

3.3.23. Starr, E., Berument, S.K., Pickles, A., Tomlins, M., Bailey, A., Papanikolaou, K., Rutter, M. "A family genetic study of autism associated with profound mental retardation." *J Autism Dev Disord* 2001 Feb;31(1):89-96.

Medical Research Council Child Psychiatry Unit, Institute of Psychiatry, London, United Kingdom.

We sought to determine if the family loading for either the broader autism phenotype or for cognitive impairment differed according to whether or not autism was accompanied by severe mental retardation. The sample comprised 47 probands with autism meeting ICD-10 criteria, as assessed by the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule. Family history interview and findings were compared with those for the higher IQ autism and Down syndrome samples in the Bolton et al. (1994) study. The familial loading for autism and for the broader phenotype was closely comparable to that in the study of higher IQ autism, and different from that for Down syndrome. The family loading for scholastic achievement difficulties was slightly, but significantly, higher when autism was accompanied by severe retardation.

3.3.24. Robertson, J., Emerson, E., Gregory, N., Hatton, C., Kessissoglou, S., Hallam, A., Linehan, C. "Social networks of people with mental retardation in residential settings." *Ment Retard* 2001 Jun;39(3):201-14.

Institute for Health Research, Lancaster University, Lancaster LA1 4YT, UK.

Information was collected on the social networks of 500 adults with mental retardation receiving different types of residential supports. Results indicated that (a) the reported median size of participants' social networks (excluding staff) was 2 people; (b) 83% of participants were reported to have a staff member; 72%, a member of their family; 54%, another person with mental retardation; and 30%, a person who did not fit into any of these categories in their social network; (c) variation in the size and composition of participants' social networks was associated with a range of variables, including the personal characteristics of residents (age, autism, ability, and challenging behavior), the type of previous and current accommodation, staffing ratios, institutional climate, and the implementation of "active support."

3.3.25. Dobson, S., Upadhyaya, S., McNeil, J., Venkateswaran, S., Gilderdale, D. "Developing an information pack for the Asian carers of people with autism spectrum disorders." *Int J Lang Commun Disord* 2001;36 Suppl:216-21.

Listonshiels Day Centre, Bradford Community NHS Trust, Bierley Lane, Bradford BD4 6DN. dobson@bcht.northy.nhs.uk

An investigation is described which forms the basis for the development of an information package for the Asian carers

of people with autism spectrum disorders (ASD) and learning disabilities. The results of semi-structured interviews and planning for questionnaires with three different linguistic Asian groups (Urdu, Gujarati and Bengali) are presented. The views, attitudes and awareness of autism, knowledge of support services and perceived priority of needs are analysed for the three different communities. The investigation concludes with recommendations as to whether separate information is needed by each culture or whether a single information pack can be used and presented in each language format. The possible presentation format in which the information can be produced is also discussed.

3.3.26. Briskman, J., Happe, F., Frith, U. "Exploring the cognitive phenotype of autism: weak "central coherence" in parents and siblings of children with autism: II. Real-life skills and preferences." *J Child Psychol Psychiatry* 2001 Mar;42(3):309-16.

Institute of Psychiatry, Kings College, London, UK.

Information on everyday life activities and preferences in both social and nonsocial domains was obtained from parents and children who had taken part in an experimental study of central coherence. Comparisons were made between parents who had a son with autism, parents with a dyslexic son, and families without a history of developmental disorder, as well as the male siblings in these families. Data on everyday preferences and abilities were elicited by means of an experimental questionnaire. Significant group differences in social and nonsocial preferences were found, suggesting that some parents showed similarities with their son with autism, in preference for nonsocial activities and ability in detail-focused processing. A similar experimental questionnaire, completed by parents on behalf of their sons, discriminated between autism group probands and controls, but did not differentiate sibling groups. The relevance of the nonsocial items to central coherence is discussed in the light of the findings in Part I: autism parents who reported more autism-related nonsocial (but not social) preferences, tended to show a piecemeal processing style on the experimental tasks.

3.3.27. Cade, M., Tidwell, S. "Autism and the school nurse." *J Sch Health* 2001 Mar;71(3):96-100. Publication Types: Review, Review, Tutorial.

Emporia State University, 1127 Chestnut, Emporia, KS 66801, USA.

Until recently, treatment for children with autism involved housing them in hospitals for the developmentally disabled. Today, more states are returning children with autism to their home communities, and more parents are choosing or are being required to keep their children with autism in their homes. Laws were developed to ensure that children with autism receive some form of education, often through the local school system. School nurses, who may not have experience working with children with autism, may feel uncertain about how to provide support for the child with autism. Approximately 300,000 persons in the United States have autism or display autistic behaviors. About one-third are under age 21. People with autism come from all socioeconomic

classes. Males are four times more likely to be affected by autism than females. People with autism can be expected to live a normal lifespan.

3.3.28. Committee on Children with Disabilities. "American Academy of Pediatrics: Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. Committee on Children With Disabilities." *Pediatrics* 2001 Mar;107(3):598-601. Publication Types: Guideline.

The use of complementary and alternative medicine (CAM) to treat chronic illness or disability is increasing in the United States. This is especially evident among children with autism and related disorders. It may be challenging to the practicing pediatrician to distinguish among accepted biomedical treatments, unproven therapies, and alternative therapies. Moreover, there are no published guidelines regarding the use of CAM in the care of children with chronic illness or disability. To best serve the interests of children, it is important to maintain a scientific perspective, to provide balanced advice about therapeutic options, to guard against bias, and to establish and maintain a trusting relationship with families. This statement provides information and guidance for pediatricians when counseling families about CAM.

3.3.29. Luteijn, E.F., Serra, M., Jackson, S., Steenhuis, M.P., Althaus, M., Volkmar, F., Minderaa, R. "How unspecified are disorders of children with a pervasive developmental disorder not otherwise specified? A study of social problems in children with PDD-NOS and ADHD." *Eur Child Adolesc Psychiatry* 2000 Sep;9(3):168-79.

University Centre of Child and Adolescent Psychiatry, Groningen, The Netherlands.

This study examines possible differences and similarities between social behaviour problems in children with problems classified as pervasive developmental disorder not otherwise specified (PDD-NOS) and a group of children with problems classified as ADHD, as measured by parent questionnaires. The instruments involved were the CBCL (Child Behaviour Checklist), the ABC (Autism Behaviour Checklist) and a new instrument: the CSBQ (Children's Social Behaviour Questionnaire). In comparing the PDD-NOS group and the ADHD group, the results show that, according to parent reports, both groups have severe problems in executing appropriate social behaviour, but the PDD-NOS group can be distinguished from the ADHD group by the nature and the extent of these problems. The PDD-NOS group had significantly more social problems (as measured by the CBCL Social scale), withdrawn problems (as measured by the CBCL Withdrawn scale) and PDD-specific problems (as measured on the ABC Relating scale, the ABC Language scale, the CSBQ total score, the CSBQ Social Interaction scale and CSBQ Communication scale). In addition, although the descriptions of the social problems are global, i.e. on scale level, the results also show that the social problems of PDD-NOS children can be positively formulated and described as at least including severe social interaction problems, withdrawn behaviours and communication problems.

3.3.30. Klin, A. "Attributing social meaning to ambiguous visual stimuli in higher-functioning autism and Asperger syndrome: The Social Attribution Task." *J Child Psychol Psychiatry* 2000 Oct;41(7):831-46.

Yale Child Study Center, Yale University School of Medicine, New Haven, CT 06520, USA. Ami.Klin@Yale.Edu

More able individuals with autism and Asperger syndrome (AS) have been shown to pass relatively high level theory of mind (ToM) tasks without displaying commensurate levels of social adaptation in naturalistic settings. This paper presents a social cognitive procedure the Social Attribution Task (SAT) that reduces factors thought to facilitate ToM task performance without facilitating real-life social functioning. Sixty participants with autism (N = 20), AS (N = 20), and normally developing adolescents and adults (N = 20) with normative IQs were asked to provide narratives describing Heider and Simmel's (1944) silent cartoon animation in which geometric shapes enact a social plot. These narratives were coded in terms of the participants' abilities to attribute social meaning to the geometric cartoon. The SAT provides reliable and quantified scores on seven indices of social cognition. Results revealed marked deficits in both clinical groups across all indices. These deficits were not related to verbal IQ or level of metalinguistic skills. Individuals with autism and AS identified about a quarter of the social elements in the story, a third of their attributions were irrelevant to the social plot, and they used pertinent ToM terms very infrequently. They were also unable to derive psychologically based personality features from the shapes' movements. When provided with more explicit verbal information on the nature of the cartoon, individuals with AS improved their performance slightly more than those with autism, but not significantly so.

3.3.31. Heavey, L., Phillips, W., Baron-Cohen, S., Rutter, M. "The Awkward Moments Test: a naturalistic measure of social understanding in autism." *J Autism Dev Disord* 2000 Jun;30(3):225-36.

MRC Child Psychiatry Unit, Institute of Psychiatry, Denmark Hill, London, England. spjwljh@iop.kcl.ac.uk

Details are given of a new advanced theory of mind task, developed to approximate the demands of real-life mentalizing in able individuals with autism. Excerpts of films showing characters in social situations were presented, with participants required to answer questions on characters' mental states and on control, nonsocial questions. When compared with control participants, adults with high-functioning autism and Asperger syndrome were most impaired in their ability to answer the questions requiring mind-reading ability. Although the present findings have implications for task modification, such naturalistic, dynamic stimuli are held to offer an important means of studying subtle difficulties in mentalistic understanding.

3.3.32. Hwang, B., Hughes, C. "The effects of social interactive training on early social communicative skills of children with autism." *J Autism Dev Disord* 2000 Aug;30(4):331-43. Publication Types: Review, Review, Tutorial.

Vanderbilt University, Nashville, Tennessee 37203, USA.

Growing attention has been directed at the relation between early social communicative skills of children with autism and subsequent development of these children's social and communicative functioning. We reviewed 16 empirical studies that investigated the effects of social interactive interventions designed to increase early social communicative skills of young children with autism by increasing their role as initiator of social interactions. To identify factors relating to treatment effectiveness, we analyzed studies in relation to participant characteristics, settings, target behaviors, training methods, and results. To determine durability of treatment, we analyzed generalization effects across persons, settings, stimuli, and time. Increases were found for social and affective behaviors, nonverbal and verbal communication, eye contact, joint attention, and imitative play. Limited generalization or maintenance of target behaviors was reported. Findings are discussed in relation to critical variables that may relate to treatment effectiveness in future research and practice efforts.

3.3.33. Emery, N.J. "The eyes have it: the neuroethology, function and evolution of social gaze." *Neurosci Biobehav Rev* 2000 Aug;24(6):581-604. Publication Types: Review, Review, Academic.

Center for Neuroscience, Department of Psychiatry & California Regional Primate Research Center, University of California, Davis, CA 95616, USA. njemery@ucdavis.edu

Gaze is an important component of social interaction. The function, evolution and neurobiology of gaze processing are therefore of interest to a number of researchers. This review discusses the evolutionary role of social gaze in vertebrates (focusing on primates), and a hypothesis that this role has changed substantially for primates compared to other animals. This change may have been driven by morphological changes to the face and eyes of primates, limitations in the facial anatomy of other vertebrates, changes in the ecology of the environment in which primates live, and a necessity to communicate information about the environment, emotional and mental states. The eyes represent different levels of signal value depending on the status, disposition and emotional state of the sender and receiver of such signals. There are regions in the monkey and human brain which contain neurons that respond selectively to faces, bodies and eye gaze. The ability to follow another individual's gaze direction is affected in individuals with autism and other psychopathological disorders, and after particular localized brain lesions. The hypothesis that gaze following is "hard-wired" in the brain, and may be localized within a circuit linking the superior temporal sulcus, amygdala and orbitofrontal cortex is discussed.

3.3.34. Bauminger, N., Kasari, C. "Loneliness and friendship in high-functioning children with autism." *Child Dev* 2000 Mar-Apr;71(2):447-56.

School of Education, Bar-Ilan University, Ramat-Gan, Israel. bauminn@mail.biu.ac.il

Loneliness and friendship were examined in 22 high-functioning children with autism and 19 typically developing children equated with the autistic children for IQ, CA, gender, mother's education, and ethnicity. Children between the ages of 8 and 14 were asked to report on both their understanding and feelings of loneliness and the quality of their friendship. Compared to typically developing children, children with autism were both lonelier and had less complete understandings of loneliness. Although all children with autism reported having at least one friend, the quality of their friendships was poorer in terms of companionship, security, and help. Fewer associations were found between loneliness and friendship for the autistic than for the non-autistic children, suggesting less understanding of the relation between loneliness and friendship. Implications of these results are discussed for conceptualizing the social deficits in autism.

3.3.35. Glasberg, B.A. "The development of siblings' understanding of autism spectrum disorders." *J Autism Dev Disord* 2000 Apr;30(2):143-56.

The Douglass Developmental Disabilities Center, Rutgers, the State University of New Jersey, Piscataway 08854, USA.

While professionals commonly advocate sharing information about autism spectrum disorders with siblings, no guidelines currently exist that describe what types of information might be relevant for siblings at different ages. To address this issue, the interviewing method described by Bibace and Walsh (1979, 1980), which measures cognitive sophistication in thinking about illness, was adapted to examine perspectives on autism spectrum disorders. Sixty-three siblings of individuals with autism or related disorders were interviewed using this measure. Parents were given the same interview as their child, and asked to predict their child's responses. Children's reasoning became more mature with age, but developed at a delayed rate compared to norms for illness concepts. Although accurate in estimating their child's understanding of the definition and cause of their sibling's diagnosis, parents tended to overestimate their child's understanding of the disorder's impact.

3.3.36. Zwaigenbaum, L., Szatmari, P., Mahoney, W., Bryson, S., Bartolucci, G., MacLean, J. "High functioning autism and Childhood Disintegrative Disorder in half brothers." *J Autism Dev Disord* 2000 Apr;30(2):121-6.

Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada. zwaigenb@fhs.mcmaster.ca

Childhood Disintegrative Disorder (CDD) is grouped with autism as a subtype of Pervasive Developmental Disorder (PDD) in ICD-10 and DSM-IV. This is the first report of autism and CDD cosegregating within a sibship. J. P. and M. P. are half-brothers with the same mother. J. P. is an 18-year-old with impairments in communication, social reciprocity, and stereotypies and was diagnosed with autism. M. P. is a 7-year-old who developed normally to 2 years 4 months. He then underwent a profound regression, becoming nonverbal and socially withdrawn, and lost adaptive skills.

Investigations did not reveal any neurodegenerative process. M. P. was diagnosed with CDD. The rarity of the two conditions suggests a shared transmissible mechanism. The implications for autism/PDD genetic studies are discussed.

3.3.37. Constantino, J.N., Przybeck, T., Friesen, D., Todd, R.D. "Reciprocal social behavior in children with and without pervasive developmental disorders." *J Dev Behav Pediatr* 2000 Feb;21(1):2-11.

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA. constantino@psychiatry.wustl.edu

An invariant feature of pervasive developmental disorders (PDDs) is a relative deficit in the capacity for reciprocal social behavior (RSB). The authors acquired teacher reports of RSB in 287 schoolchildren and parent reports of RSB in 158 child psychiatric patients using a new research instrument, the Social Reciprocity Scale. Total scores on this measure of RSB were continuously distributed in all groups of subjects; children with PDDs scored significantly higher for the degree of deficits in RSB than did clinical or nonclinical controls. Latent class analysis and factor analysis failed to demonstrate separate categories of deficiency for core autistic symptomatology and more general impairments in RSB, consistent with the notion of a "broader autism phenotype." Assessments of RSB on a continuous scale may be useful clinically for characterizing the behavior of children whose social deficits fall below the threshold for a full diagnosis of autism. They may also be useful in genetic-linkage studies of autistic spectrum disorders.

3.3.38. Stella, J., Mundy, P., Tuchman, R. "Social and nonsocial factors in the Childhood Autism Rating Scale." *J Autism Dev Disord* 1999 Aug;29(4):307-17.

Department of Psychology, University of Miami, Coral Gables, Florida 33124, USA.

The Childhood Autism Rating Scale (CARS) was factor analyzed to determine if distinct and independent "subgroups" of symptoms could be derived, which would be consistent with the current multidimensional theory and nosology for autism. To address this issue, the CARS was factor analyzed for a sample of 90 children with diagnoses of either autism or PDDNOS, based on DSM-III-R diagnostic criteria. Five factors emerged: Social Communication, Emotional Reactivity, Social Orienting, Cognitive and Behavioral Consistency, and Odd Sensory Exploration. Factor-based scales were created. These factor-based scales were demonstrated to distinguish subjects with autism from subjects with PDDNOS and nonautistic subjects. Factor-based scores were examined to determine the degree to which they were associated with individual differences (such as age, IQ, gender, history of regression, and history of abnormal EEGs) among children with pervasive developmental disorders (PDDs). The application of these distinct and independent factors may have important clinical and research implications. The generation of factor-based scales may provide information on the nature of the individual differences that are thought to

be present among children with autism. Additionally, the use of factor-based scale scores may increase the sensitivity of the CARS for identifying younger and/or higher functioning individuals within the PDD spectrum.

3.3.39. Njardvik, U., Matson, J.L., Cherry, K.E. "A comparison of social skills in adults with autistic disorder, pervasive developmental disorder not otherwise specified, and mental retardation." *J Autism Dev Disord* 1999 Aug;29(4):287-95.

Louisiana State University, Baton Rouge 70803-5501, USA.

We examined the social skills of adults with autism, PDDNOS, and mental retardation. All participants were diagnosed with profound mental retardation. Participants in the autism and PDDNOS groups had been previously diagnosed using the Childhood Autism Rating Scale (CARS) and record review. These diagnoses were confirmed by readministering the CARS by one author and an independent rater. Social skills were assessed by using the Vineland Adaptive Behavior Scales and the Matson Evaluation of Social Skills in the Severely Retarded. Significant differences between the autism and mental retardation groups were found on both measures. The PDDNOS group demonstrated better positive nonverbal social skills than the autism group but not the mental retardation group. Special treatment needs of institutionalized adults with autism appear warranted along with a need to clarify further the differences between PDDNOS and mental retardation.

3.3.40. Sigman, M., Ruskin, E., Arbeile, S., Corona, R., Dissanayake, C., Espinosa, M., Kim, N., Lopez, A., Zierhut, C. "Continuity and change in the social competence of children with autism, Down syndrome, and developmental delays." *Monogr Soc Res Child Dev* 1999;64(1):1-114.

Department of Psychiatry, UCLA School of Medicine 90024, USA.

The aims of this longitudinal study were: (1) to assess the continuity and change in diagnosis, intelligence, and language skills in children with autism, Down syndrome, and other developmental delays, (2) to specify the deficits in social competence and language skills in these children, and (3) to identify precursors in the preschool period of gains in language skills and of peer engagement in the mid-school years. The initial sample consisted of 70 children with autism, 93 children with Down syndrome, 59 children with developmental delays, and 108 typically developing children, with the first three groups of children studied when they were between 2 and 6 years of age. At follow-up, 51 children with autism, 71 children with Down syndrome, and 33 children with developmental delays were assessed at mean ages around 10-13 years. The long-term follow-up showed little change in the diagnosis of autism but sizeable improvements in intellectual and language abilities within the autistic group, a pattern that was not seen in the children with Down syndrome. Unique deficits in joint attention, some forms of representational play, responsiveness to the emotions of others, and initiation of peer engagement were identified in

the autistic children, whereas the children with Down syndrome seemed to have a specific deficit only in language. Joint attention skills were concurrently associated with language abilities in all groups and predicted long-term gains in expressive language for the children with autism. Children with autism, regardless of their level of functioning, were less socially engaged with classmates than the other developmentally disabled children because they infrequently initiated and accepted play bids, not because they were rebuffed by peers. Early nonverbal communication and play skills were predictors of the frequency of initiations of peer play for the children with Down syndrome as well as the extent of peer engagement of the children with autism. These results suggest that improvements in early communication and play skills may have long-term consequences for later language and social competence in these groups of children.

3.3.41. Realmuto, G.M., Ruble, L.A. "Sexual behaviors in autism: problems of definition and management." *J Autism Dev Disord* 1999 Apr;29(2):121-7.

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Surveys of sexual behavior in autism suggest a variety of behavioral expression. However, the course of sexual development in autism is unplotted, leaving questions about the normalcy of specific behaviors. Even less is known about deviations of sexual development and the incidence of paraphilias in this population. We explore the problems of definition of sexual behaviors and describe a case report that highlights the difficulties of management. An application of a testosterone-suppressing medication and its effect on sexual behavior are reported. After failure of behavioral and educational programs, leuprolide, an injectable antiandrogen, resulted in suppression of behaviors and retention of the participants' community placement. Follow-up for almost 3 years shows no abnormal physical effects. Dosage has been tapered over that period to a low but effective dose. Directions for research are discussed.

3.3.42. Trillingsgaard, A. "The script model in relation to autism." *Eur Child Adolesc Psychiatry* 1999 Mar;8(1):45-9.

Institute of Psychology, University of Aarhus, Denmark.

The primary purpose of this study was to investigate autistic children's scripts for social routines. Scripts specify familiar events in terms of who does what, when, to whom, and why. Scripts are verbalizations of mental event representations, containing and organizing generalized knowledge of how the world works. Scripts are presumed to be of vital importance for the development of shared meaning, communication, and social behaviour. In this study, children with autism were asked to explain well-known social routines, such as how you shop in a supermarket, make a cake or celebrate a birthday. The scripts of the 12 children with non-retarded autism were compared to scripts of matched normal control children. Despite the fact that all of the participating children with autism had an IQ above 90 and a mental age between 8 and

14, a significant difference in autistic and normal control children's ability to generate scripts for familiar social routines was found. The results are discussed in relation to the same children's ability to pass theory-of-mind tests and their verbal intelligence.

3.3.43. Kohn, Y., Fahum, T., Ratzoni, G., Apter, A. "Aggression and sexual offense in Asperger's syndrome." *Isr J Psychiatry Relat Sci* 1998;35(4):293-9.

Psychiatry Department, Hadassah University Hospital, Hebrew University-Hadassah School of Medicine, Jerusalem, Israel.

Asperger's Syndrome is one of the diagnostic subcategories of pervasive developmental disorders. It is characterized by a defect in reciprocal social interaction, lack of empathy for others and poor non-verbal communication. Antisocial acts, including aggression and sexual offense, are not considered to be common in this disorder. We describe an adolescent with Asperger's Syndrome whose main problems are his violence and sexual offenses. We assume that these symptoms are secondary to his diagnosis of Asperger's as a manifestation of his difficulties with the "theory of mind" of others. This atypical case report is in contrast with the low prevalence of aggression and sexual offense in Asperger's, as reported in the literature. We discuss the reasons for this low prevalence. Our conclusions are based on one case history and a literature review. We call for further research in this field.

3.3.44. Dawson, G., Meltzoff, A.N., Osterling, J., Rinaldi, J., Brown, E. "Children with autism fail to orient to naturally occurring social stimuli." *J Autism Dev Disord* 1998 Dec;28(6):479-85.

Department of Psychology, University of Washington, Seattle 98195, USA.

Children with autism were compared to developmentally matched children with Down syndrome or typical development in terms of their ability to visually orient to two social stimuli (name called, hands clapping) and two nonsocial stimuli (rattle, musical jack-in-the-box), and in terms of their ability to share attention (following another's gaze or point). It was found that, compared to children with Down syndrome or typical development, children with autism more frequently failed to orient to all stimuli, and that this failure was much more extreme for social stimuli. Children with autism who

oriented to social stimuli took longer to do so compared to the other two groups of children. Children with autism also exhibited impairments in shared attention. Moreover, for both children with autism and Down syndrome, correlational analyses revealed a relation between shared attention performance and the ability to orient to social stimuli, but no relation between shared attention performance and the ability to orient to nonsocial stimuli. Results suggest that social orienting impairments may contribute to difficulties in shared attention found in autism.

3.3.45. Konstantareas, M.M. "Allegations of sexual abuse by nonverbal autistic people via facilitated communication: testing of validity." *Child Abuse Negl* 1998 Oct;22(10):1027-41. Publication Types: Review, Review, Tutorial.

University of Guelph, Ontario, Canada.

OBJECTIVE: The aim of the paper is to offer a comprehensive approach to establishing the validity of allegations of sexual abuse by nonverbal autistic children and adults produced through facilitated communication (FC). This approach is offered as an alternative to existing methodology that relies exclusively on the "message passing" task, and has been used to advantage in the courts. **METHOD:** Three components to the battery are included: (a) specialized psychometric testing; (b) a variant of the message passing task; and (c) systematic analysis of the allegations themselves. Through the juxtaposition of the data from the different sources, conclusions can be reached as to the allegations' authorship. **RESULTS:** The results of a series of studies addressing the issue of validity of FC in general are briefly presented. Then a case presentation is offered to demonstrate how the technique can be employed to clarify allegations of sexual abuse. Elements of two other cases are also briefly discussed. **CONCLUSIONS:** Facilitated communication has been heralded as a breakthrough, allowing nonverbal people with autism to express themselves. It relies on manual guidance by a facilitator. Its proponents' resistance to allowing the technique's validation relying on the paradigm of normal science has resulted in its broad dissemination without support. In the case of sexual abuse allegations thus far the "message passing" task has been used to assess their verity. The present methodology is offered as a more comprehensive alternative to "message passing," with relevance to other populations of nonverbal individuals.

MANAGEMENT

Medical

4.1.1. Coplan, J., Souders, M.C., Mulberg, A.E., Belchic, J.K., Wray, J., Jawad, A.F., Gallagher, P.R., Mitchell, R., Gerdes, M., Levy, S.E. "Children with autistic spectrum disorders. II: parents are unable to distinguish secretin from placebo under double-blind conditions." *Arch Dis Child*. 2003 Aug;88(8):737-9. Publication Types: Clinical Trial, Randomized Controlled Trial.

Division of Child Development and Rehabilitation, Children's Seashore House of The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.

BACKGROUND: Standardised measures of behaviour have failed to detect short term improvement in children with autism following treatment with secretin. However, it is possible that standardised measures are insensitive to dimensions of child behaviour that are nonetheless detectable by parents. **AIM:** To determine the ability of parents of children with autism to guess, under double blind conditions, whether their child had received secretin or placebo. **METHODS:** 2x2 crossover randomised blinded study, comparing the effect of synthetic human secretin 2 U/kg to placebo (saline). Sixty two children with autism (aged 43-103 months) were randomly allocated to two groups: group 1 received placebo, followed six weeks later by secretin, and group 2 received secretin followed by placebo. At the conclusion of the study, parents were asked to guess their child's group assignment. **RESULTS:** Twenty seven families guessed their child's group assignment correctly and 27 guessed incorrectly. In 48 instances, parents based their guess on perceived improvement; in six cases, parents based their guess on perceived deterioration. Six families saw no difference after either infusion, and offered no guess. One family dropped out after the first infusion, and one family was lost to follow up after the second infusion. **CONCLUSION:** In a controlled setting, parents of young children with autism are unable to distinguish the short term behavioural effects of secretin from placebo.

4.1.2. Levy, S.E., Souders, M.C., Wray, J., Jawad, A.F., Gallagher, P.R., Coplan, J., Belchic, J.K., Gerdes, M., Mitchell, R., Mulberg, A.E. "Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin." *Arch Dis Child*. 2003 Aug;88(8):731-6. Publication Types: Clinical Trial, Randomized Controlled Trial.

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AIMS: To examine the effect of a single dose of human synthetic secretin (HSS) on behaviour and communication in children with autism spectrum disorder (ASD) using an objective measure of communication and social reciprocity and standardized rating scales. **METHODS:** Randomised, crossover, double blind, and placebo controlled trial of a single intravenous dose of human synthetic secretin (HSS) 2 CU/kg. The 62 subjects (3-8 years) were assigned to group 1 (saline placebo/HSS) or group 2 (HSS/saline placebo). Diagnosis was confirmed by ADI-R (Autism Diagnostic Interview-Revised)

algorithm. Severity of symptoms was rated using the CARS (Childhood Autism Rating Scale). Outcome measures included Communication and Symbolic Behavior Scale (CSBS), Ritvo Real-life Rating Scale, weekly Global Rating Scale (GBRS) by parents and teachers, and daily log of gastrointestinal symptoms. The communication subscale of the CSBS, specifying communication function, reciprocity, and social-affective signalling was videotaped and scored by a blinded, trained observer. **RESULTS:** Sixty one children completed the study. After randomisation, there were no significant differences in gender, race, age, and parent and teacher GBRS and Ritvo Scale between the two groups. Compared with placebo, secretin treatment was not associated with significant improvement of CSBS standard scores from baseline to 2 or 4 weeks post-infusion. Five children showed clinical improvement in standard scores: two after HSS and three after placebo. There were no significant changes in gastrointestinal symptoms after HSS or saline placebo. **CONCLUSIONS:** A single dose of intravenous human secretin is not effective in changing behaviour and communication in children with ASD when compared to placebo.

4.1.3. Lerman, D.C., Kelley, M.E., Vorndran, C.M., Van Camp, C.M. "Collateral effects of response blocking during the treatment of stereotypic behavior." *J Appl Behav Anal*. 2003 Spring;36(1):119-23. Publication Types: Evaluation Studies.

Louisiana State University, The Louisiana Center for Excellence in Autism, Baton Rouge 70803, USA. dlerman@lsu.edu

The collateral effects of response blocking were evaluated while treating stereotypic behavior in a woman diagnosed with autism. Blocking stereotypic behavior (head and tooth capping) was associated with decreases in leisure-item interaction and increases in another stereotypic response (hand wringing). Results suggested that the reduction in item interaction was due to adventitious punishment. Prompts to access an alternative source of reinforcement attenuated the side effects somewhat, but results suggested that the undesirable effects of response blocking may be fairly durable.

4.1.4. Moore, V., Goodson, S. "How well does early diagnosis of autism stand the test of time? Follow-up study of children assessed for autism at age 2 and development of an early diagnostic service." *Autism*. 2003 Mar;7(1):47-63.

Tremona Road Children's Centre, Southampton, UK. Vanessa.Moore@scpct.nhs.uk

Twenty children who presented with severe and communication difficulties at age 2 underwent a comprehensive assessment for autism, and were reassessed at age 4-5. In common with other recent studies, diagnosis of autistic spectrum disorders at age 2 was found to be reliable and stable. The communication and social skills of the children showed little change overall by the second assessment. However, children whose scores deteriorated in the social domain tended to have presented initially with more significant behaviour problems. Few repetitive behaviours were observed at age 2, whereas these were more apparent

by age 4-5. The finding that early diagnosis of autism is reliable and stable has led to the development of an early diagnostic service in Southampton, which is described. The importance of early diagnosis is that it opens the door to early intervention programmes, which in turn prevent many problems from occurring in later life.

4.1.5. Hunter, L.C., O'Hare, A., Herron, W.J., Fisher, L.A., Jones, G.E. "Opioid peptides and dipeptidyl peptidase in autism." *Dev Med Child Neurol.* 2003 Feb;45(2):121-8.

YAbA Ltd, Logan Building, Roslin Biocentre, Midlothian, UK.

It has been hypothesized that autism results from an 'opioid peptide excess'. The aims of this study were to (1) confirm the presence of opioid peptides in the urine of children with autism and (2) determine whether dipeptidyl peptidase IV (DPPIV/CD26) is defective in children with autism. Opioid peptides were not detected in either the urine of children with autism (10 children; nine males, one female; age range 2 years 6 months to 10 years 1 month) or their siblings (10 children; seven males, three females; age range 2 years 3 months to 12 years 7 months) using liquid chromatography-ultraviolet-mass spectrometric analysis (LC-UV-MS). Plasma from 11 normally developing adults (25 years 5 months to 55 years 5 months) was also tested. The amount and activity of DPPIV in the plasma were quantified by an ELISA and DPPIV enzyme assay respectively; DPPIV was not found to be defective. The percentage of mononuclear cells expressing DPPIV (as CD26) was determined by flow cytometry. Children with autism had a significantly lower percentage of cells expressing CD3 and CD26, suggesting that they had lower T-cell numbers than their siblings. In conclusion, this study failed to replicate the findings of others and questions the validity of the opioid peptide excess theory for the cause of autism.

4.1.6. Diggle, T., McConachie, H.R., Randle, V.R. "Parent-mediated early intervention for young children with autism spectrum disorder." *Cochrane Database Syst Rev.* 2003;(1):CD003496. Publication Types: Review, Review, Academic.

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BACKGROUND: Recent estimates concerning the prevalence of autistic spectrum disorder are much higher than those reported 30 years ago, with at least 1 in 400 children affected. This group of children and families have important service needs. The involvement of parents in implementing intervention strategies designed to help their autistic children has long been accepted as helpful. The potential benefits are increased skills and reduced stress for parents as well as children. **OBJECTIVES:** The objective of this review was to determine the extent to which parent-mediated early intervention has been shown to be effective in the treatment of children aged 1 year to 6 years 11 months with autistic spectrum disorder. In particular, it aimed to assess the effectiveness of such interventions in terms of the benefits for both children and their parents. **SEARCH STRATEGY:** A range

of psychological, educational and biomedical databases were searched. Bibliographies and reference lists of key articles were searched, field experts were contacted and key journals were hand searched. **SELECTION CRITERIA:** Only randomised or quasi-randomised studies were included. Study interventions had a significant focus on parent-implemented early intervention, compared to a group of children who received no treatment, a waiting list group or a different form of intervention. There was at least one objective, child related outcome measure. **DATA COLLECTION AND ANALYSIS:** Appraisal of the methodological quality of included studies was carried out independently by two reviewers. Differences between the included studies in terms of the type of intervention, the comparison groups used and the outcome measures were too great to allow for direct comparison. **MAIN RESULTS:** The results of this review are based on data from two studies. Two significant results were found to favour parent training in one study: child language and maternal knowledge of autism. In the other, intensive intervention (involving parents, but primarily delivered by professionals) was associated with better child outcomes on direct measurement than were found for parent-mediated early intervention, but no differences were found in relation to measures of parent and teacher perceptions of skills and behaviours. **REVIEWER'S CONCLUSIONS:** This review has little to offer in the way of implications for practice: there were only two studies, the numbers of participants included were small, and the two studies could not be compared directly to one another. In terms of research, randomised controlled trials involving large samples need to be carried out, involving both short and long-term outcome information and full economic evaluations. Research in this area is hampered by barriers to randomisation, such as availability of equivalent services.

4.1.7. Towbin, K.E. "Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome." *Child Adolesc Psychiatry Clin N Am.* 2003 Jan;12(1):23-45.

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The treatment of complex, polymorphous disorders like HFA/AS always brings a particular challenge to pharmacotherapy. Additionally, the specific characteristics presented by HFA/AS introduce unique complications to patient care and place unusual demands on a clinician's skill and experience. To provide safe and effective treatment, the clinician must understand the core features of the disorder and the manifestations of the condition in his or her patient. Furthermore, a thorough understanding of the family, school, and community resources and limitations is necessary. Once an assessment has been made, focusing on target symptoms provides a crucial framework for care. Knowing manifestations of symptoms and characterizing their distribution and behavior in that patient is most important. For patients with HFA/AS it is particularly essential to coordinate behavioral and pharmacologic objectives. The

target symptoms should be tracked carefully and placed into a priority system that is based on the risks and disability they create for the patient. The skill of pharmacotherapy also means setting out realistic expectations, keeping track of the larger systems of care at school and home, and collaboration with parents and care providers. There is an expanding range and pace of biologic and intervention research into HFA/AS. The genetic work has produced exciting leads that are likely to be helpful to future generations [82-84], but the task of clinicians is to tend to today's patients. As we discover more about the complex neural circuitry subserving repetitive behaviors, reward systems, and social cognition, there are good reasons to believe our treatments will become more sophisticated and specific. Psychopharmacology is also moving to design medications that target more specific populations of receptor and brain functions. This is likely to produce medicines that have fewer side effects, are more effective, and are more symptom-specific. Pharmacotherapy is not the ultimate treatment for HFA/AS but it has a definite place. Medication can be a critical element in a comprehensive treatment plan. There is a wider range of medications with more specific biologic effects than ever before. For patients with HFA/AS these newer agents are safer and less disruptive. When paired with clinicians who are becoming more skilled at recognizing and managing symptoms, patients have a greater opportunity to reach their potential and lead pleasurable lives.

4.1.8. Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C.M., Aronowitz, B.R., Mosovich, S. "Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders." *Neuropsychopharmacology*. 2003 Jan;28(1):193-8. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Autism is a neurodevelopmental disorder characterized by dysfunction in three core behavioral domains: repetitive behaviors, social deficits, and language abnormalities. There is evidence that abnormalities exist in peptide systems, particularly the oxytocin system, in autism spectrum patients. Furthermore, oxytocin and the closely related peptide vasopressin are known to play a role in social and repetitive behaviors. This study examined the impact of oxytocin on repetitive behaviors in 15 adults with autism or Asperger's disorder via randomized double-blind oxytocin and placebo challenges. The primary outcome measure was an instrument rating six repetitive behaviors: need to know, repeating, ordering, need to tell/ask, self-injury, and touching. Patients with autism spectrum disorders showed a significant reduction in repetitive behaviors following oxytocin infusion in comparison to placebo infusion. Repetitive behavior in autism spectrum disorders may be related to abnormalities in the oxytocin system, and may be partially ameliorated by synthetic oxytocin infusion.

4.1.9. Langworthy-Lam, K.S., Aman, M.G., Van Bourgondien, M.E. "Prevalence and patterns of use of psychoactive medicines in individuals with autism in the Autism Society of North Carolina." *J Child Adolesc Psychopharmacol*. 2002 Winter;12(4):311-21.

The Nisonger Center for Mental Retardation and Developmental Disabilities, The Ohio State University, Columbus, Ohio 43210, USA.

The aim of this study was to assess the prevalence and patterns of psychoactive and over-the-counter medicines in a large cohort of individuals with autism. We conducted a mail survey of 3,228 families that are members of the Autism Society of North Carolina. This is one of the largest chapters of the Autism Society of America. The survey form addressed current medicines used, side effects, demographic characteristics, and medical conditions. Some 1,538 member families within the society (48%) responded to the survey. In all, 703 (45.7%) individuals with autism were taking psychotropic drugs, 191 (12.4%) antiepileptic drugs (AEDs), and 86 (5.7%) supplements for autism. The total number taking psychotropic, antiepileptic, or vitamin treatments was 816 (53.1%). Antidepressants (taken by 21.7% of the sample), antipsychotics (16.8%), and stimulants (13.9%) were the most commonly prescribed agents. Univariate and multivariate analyses were conducted to examine factors associated with treatment. Greater age, more severe autism and mental retardation, and more restricted housing were often associated with greater use of psychoactive agents. These findings suggest that individuals with autism are a frequently medicated group, although the empirical research support for most agents being used is still very limited.

4.1.10. Chez, M.G., Buchanan, C.P., Aimonovitch, M.C., Becker, M., Schaefer, K., Black, C., Komen, J. "Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders." *J Child Neurol*. 2002 Nov;17(11):833-7. Publication Types: Clinical Trial, Randomized Controlled Trial.

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L-Carnosine, a dipeptide, can enhance frontal lobe function or be neuroprotective. It can also correlate with gamma-aminobutyric acid (GABA)-homocarnosine interaction, with possible anticonvulsive effects. We investigated 31 children with autistic spectrum disorders in an 8-week, double-blinded study to determine if 800 mg L-carnosine daily would result in observable changes versus placebo. Outcome measures were the Childhood Autism Rating Scale, the Gilliam Autism Rating Scale, the Expressive and Receptive One-Word Picture Vocabulary tests, and Clinical Global Impressions of Change. Children on placebo did not show statistically significant changes. After 8 weeks on L-carnosine, children showed statistically significant improvements on the Gilliam Autism Rating Scale (total score and the Behavior, Socialization, and Communication subscales) and the Receptive One-Word Picture Vocabulary test (all $P < .05$). Improved trends were

noted on other outcome measures. Although the mechanism of action of L-carnosine is not well understood, it may enhance neurologic function, perhaps in the enterorhinal or temporal cortex.

4.1.11. Molloy, C.A., Manning-Courtney, P., Swayne, S., Bean, J., Brown, J.M., Murray, D.S., Kinsman, A.M., Brasington, M., Ulrich, C.D. 2nd. "Lack of benefit of intravenous synthetic human secretin in the treatment of autism." *J Autism Dev Disord.* 2002 Dec;32(6):545-51. Publication Types: Clinical Trial, Randomized Controlled Trial.

Division of Developmental Disabilities, Department of Pediatrics, University of Cincinnati College of Medicine, OH, USA. cynthia.molloy@chmcc.org

The objective of this study was to determine if an intravenous infusion of synthetic human secretin improves language and behavioral symptoms in children with autism. Forty-two children with the diagnosis of autism were randomized to one of two groups in this double-blind cross-over trial. One group received 2 IU/kg of intravenous synthetic human secretin at the first visit, followed by an equal volume of intravenous saline placebo at week 6. The other group received treatments in the reverse order. All children were evaluated at weeks 1, 3, 6, 9, and 12 with standardized assessments of language, behavior, and autism symptomatology. There were no significant differences in the mean scores on any measure of language, behavior, or autism symptom severity after treatment with secretin compared to treatment with placebo. The results of this study do not support secretin as a treatment for autism.

4.1.12. Moes, D.R., Frea, W.D. "Contextualized behavioral support in early intervention for children with autism and their families." *J Autism Dev Disord.* 2002 Dec;32(6):519-33.

University of California, Los Angeles, USA.

Parent education programs have become an effective mode of treatment delivery for teaching families effective behavioral strategies to manage challenging behavior in young children with autism. Functional assessment and functional communication training (FCT) are empirically validated procedures that have recently been introduced into parent education programming to help resolve challenging behaviors. The success of these procedures, however, is contingent on family members' ability to integrate them into the specific contexts in which challenging behaviors occur. Consequently, the application of these procedures in home settings necessitates consideration of the family context in the assessment and treatment planning process. A study is presented that investigated the use of information on family context (i.e., caregiving demands, family support, patterns of social interaction) to direct the assessment and intervention planning process. More specifically, information on family context was used to individualize behavioral support plans designed to support family use of functional communication training within important family routines. Through parent-investigator collaboration we individualized the manner in

which functional communication training procedures were taught and implemented so they were contextually relevant. Utilizing a multiple baseline design, the challenging behaviors and functional communication of three children with autism were monitored across baseline, intervention (i.e., FCT, and contextualized FCT), and follow-up phases. Multiple routines for each participant were selected and monitored across all phases to evaluate changes in the dependent measures within training and generalization routines. A self-report questionnaire was administered intermittently to parents to determine if consideration of family context improved the "goodness of fit" of the functional communication training treatment packages across FCT and contextualized FCT intervention phases. Results from the study indicate that consideration of family context in the assessment and intervention planning process does not jeopardize and may contribute to the stability and durability of reductions in challenging behavior achieved with functional assessment and functional communication training procedures.

4.1.13. Kidd, P.M. "Autism, an extreme challenge to integrative medicine. Part 2: medical management." *Altern Med Rev.* 2002 Dec;7(6):472-99. Publication Types: Review, Review Literature.

Autism and allied autistic spectrum disorders (ASD) present myriad behavioral, clinical, and biochemical abnormalities. Parental participation, advanced testing protocols, and eclectic treatment strategies have driven progress toward cure. Behavioral modification and structured education are beneficial but insufficient. Dietary restrictions, including removal of milk and other casein dairy products, wheat and other gluten sources, sugar, chocolate, preservatives, and food coloring are beneficial and prerequisite to benefit from other interventions. Individualized IgG or IgE testing can identify other troublesome foods but not non-immune mediated food sensitivities. Gastrointestinal improvement rests on controlling *Candida* and other parasites, and using probiotic bacteria and nutrients to correct dysbiosis and decrease gut permeability. Detoxification of mercury and other heavy metals by DMSA/DMPS chelation can have marked benefit. Documented sulfoxidation-sulfation inadequacies call for sulfur-sulfhydryl repletion and other liver p450 support. Many nutrient supplements are beneficial and well tolerated, including dimethylglycine (DMG) and a combination of pyridoxine (vitamin B6) and magnesium, both of which benefit roughly half of ASD cases. Vitamins A, B3, C, and folic acid; the minerals calcium and zinc; cod liver oil; and digestive enzymes, all offer benefit. Secretin, a triggering factor for digestion, is presently under investigation. Immune therapies (pentoxifyllin, intravenous immunoglobulin, transfer factor, and colostrum) benefit selected cases. Long-chain omega-3 fatty acids offer great promise. Current pharmaceuticals fail to benefit the primary symptoms and can have marked adverse effects. Individualized, in-depth clinical and laboratory assessments and integrative parent-physician-scientist cooperation are the keys to successful ASD management.

4.1.14. Matarazzo, E.B. "Treatment of late onset autism as a consequence of probable autoimmune processes related to chronic bacterial infection." *World J Biol Psychiatry*. 2002 Jul;3(3):162-6.

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Two cases are described of children who at first developed normally, but before the age of three developed autistic symptoms following the reactivation of a chronic otorhinolaryngologic infection. The clinical and laboratory data of the cases support the aetiological hypothesis of an autoimmune process. Adrenocorticotrophic hormone (ACTH), prescribed in the first months of the disease, cured one case. The other patient, who was two years old when autistic symptoms appeared and was treated only six years later, showed a partial but definitive improvement with the immunosuppressive treatment. This report proposes that reactivation of a chronic bacterial infection be included among the aetiologies of Late Onset Autism, and demonstrates that, when the aetiological hypothesis of an autoimmune process based on clinical and laboratory data is considered, an immunosuppressive treatment, particularly with ACTH, can be very effective and also safe.

4.1.15. Wolery, M., Garfinkle, A.N. "Measures in intervention research with young children who have autism." *J Autism Dev Disord*. 2002 Oct;32(5):463-78. Publication Types: Review, Review, Academic.

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In this paper, the outcome measures used in intervention research with young children with autism were analyzed. Two types of literature were reviewed: reports evaluating specific intervention practices and reports of complete intervention programs. A description of the types of measures used in each literature source and measurement practices reported were analyzed and described. In addition, the intervention program literature was reviewed to determine whether factors that may mediate outcomes were measured. Finally, the literature was reviewed to identify instances in which multiple risk and opportunity factors were analyzed to account for variations in outcomes.

4.1.16. Kasari, C. "Assessing change in early intervention programs for children with autism." *J Autism Dev Disord*. 2002 Oct;32(5):447-61. Publication Types: Review, Review, Academic.

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Assessing the efficacy of any intervention can be a difficult task. In the case of children with autism who require comprehensive and long-lasting interventions, the task becomes even more difficult. In this paper, intervention studies based on comprehensive interventions for young children with autism are reviewed and examined in reference to elements that are essential to a well-designed treatment study, e.g., randomization/matching procedures, and outcome measures.

Given the complexity of these comprehensive intervention programs, and the few data available on interventions with clear empirical validation, a plea is made for studies to consider the active ingredients or component parts of an intervention, e.g., number of hours, type of setting, and teaching approach. Suggestions are further made for improving future studies, including more rigorous designs, and measuring change.

4.1.17. Kemner, C., Willemsen-Swinkels, S.H., de Jonge, M., Tuynman-Qua, H., van Engeland, H. "Open-label study of olanzapine in children with pervasive developmental disorder." *J Clin Psychopharmacol* 2002 Oct;22(5):455-60.

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The effects of olanzapine on the symptomatology of children with pervasive developmental disorder with emphasis on problems of communication and the safety of the drug were investigated in a 3-month open-label, open-dosage study. Participating in the study were 25 children age 6 to 16 years with a diagnosis of either autistic disorder or pervasive developmental disorder not otherwise specified. Psychometric measures included the Clinical Global Impression of Severity/Improvement, the Aberrant Behavior Checklist, and the TARGET (a checklist of five target symptoms). Communication skills were assessed during behavioral analysis of a playroom session. Safety measures included clinical chemistry variables, electrocardiography, the SimpsonAngus Neurological Rating Scale, the Barnes Akathisia Scale, and vital signs. Twenty-three children completed the study and showed significant improvement on three subscales of the Aberrant Behavior Checklist (Irritability, Hyperactivity, and Excessive Speech) and the TARGET. The final mean dose was 10.7 mg/day. Several aspects of communication were also improved after olanzapine treatment. However, only three children were considered responders in terms of the Clinical Global Impression of Severity/Improvement scores. The most important adverse events were weight gain, increased appetite, and loss of strength. Three children showed extrapyramidal symptoms that disappeared after the dose was lowered. Thus, while olanzapine was a relatively safe medication in children, its clinical relevance in children with pervasive developmental disorder may be limited.

4.1.18. Valdovinos, M.G., Napolitano, D.A., Zarcone, J.R., Hellings, J.A., Williams, D.C., Schroeder, S.R. "Multimodal evaluation of risperidone for destructive behavior: functional analysis, direct observations, rating scales, and psychiatric impressions." *Exp Clin Psychopharmacol* 2002 Aug;10(3):268-75. Publication Types: Clinical Trial, Randomized Controlled Trial.

Schiefelbusch Institute for Lifespan Studies, University of Kansas, USA.

Risperidone, an atypical neuroleptic, has become a popular option for treating destructive behaviors of persons with

developmental disabilities. A few studies have been conducted that evaluate the effects of risperidone on destructive behavior; however, none of these studies have combined objective measures with rating scales to evaluate the effects of risperidone on destructive behavior across home and clinical settings. This study evaluated the wide range of effects of risperidone on destructive behavior of 2 persons with developmental disabilities using weekly functional analysis sessions, daily observations, hourly home data, weekly rating scales, and monthly psychiatric impressions. Results indicate that risperidone does decrease destructive behavior and that, for the most part, all of the various measures yielded similar results.

4.1.19. Posey, D.J., McDougle, C.J. "Risperidone: a potential treatment for autism." *Curr Opin Investig Drugs* 2002 Aug;3(8):1212-6. Publication Types: Review, Review, Tutorial.

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Autistic disorder (autism) is a neuropsychiatric syndrome characterized by marked deficits in reciprocal social relatedness, communication impairment and a narrow range of interests and/or repetitive behaviors. Autism is frequently associated with, but distinct from, mental retardation. It is classified as a subtype of pervasive developmental disorder (PDD) along with 'PDD not otherwise specified' (NOS) and Asperger's disorder. These disorders have in common marked impairments in social relatedness. Individuals with autism may also have other symptoms that become the primary focus of psychiatric treatment. These associated symptoms include aggression, self-injury, irritability and anxiety.

4.1.20. Wank, R. "Schizophrenia and other mental disorders require long-term adoptive immunotherapy." *Med Hypotheses* 2002 Aug;59(2):154-8.

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Many different microbial factors seem to contribute to the pathogenesis of schizophrenic and other psychiatric disorders. Activation of all T lymphocytes reactivates those downregulated by low-grade chronic infections and restores equilibrium in immune cell subpopulations. Different immune cell subpopulations express different neurotrophin receptors and produce different cytokines, particularly brain-derived neurotrophin (BDNF) and neurotrophin 3 (NT3) [M. Besser, R. Wank, *J. Immunol.* 162 (1998) 6303-6306] that appear to play a key role in schizophrenic and bipolar disorders [E. Jonsson, S. Brene, X.R. Zhang, et al., *Acta Psychiatr. Scand.* 95 (1997) 414-419; R.S. Duman, *Arch. Gen. Psychiatry* 54 (1997) 597-606; J.A. Siuciak, D.R. Lewis, S.J. Wiegand, R.M. Lindsay, *Pharmacol. Biochem. Be* 56 (1997) 131-137]. The hypothesis that adoptive immunotherapy is effective in psychiatric disorders will be supported by three case reports, in a patient with bipolar disorder, a patient with schizophrenia, and a patient with autism.

4.1.21. Lonsdale, D., Shamberger, R.J., Audhya, T. "Treatment of autism spectrum children with thiamine tetrahydrofurfuryl disulfide: a pilot study." *Neuroendocrinol Lett* 2002 Aug;23(4):303-8. Publication Types: Clinical Trial.

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OBJECTIVES: In a Pilot Study, the clinical and biochemical effects of thiamine tetrahydrofurfuryl disulfide (TFD) on autistic spectrum children were investigated. **SUBJECTS AND METHODS:** Ten children were studied. Diagnosis was confirmed through the use of form E2, a computer assessed symptom score. For practical reasons, TFD was administered twice daily for two months in the form of rectal suppositories, each containing 50 mg of TFD. Symptomatic responses were determined through the use of the computer assessed Autism Treatment Evaluation Checklist (ATEC) forms. The erythrocyte transketolase (TKA) and thiamine pyrophosphate effect (TPPE), were measured at outset and on completion of the study to document intracellular thiamine deficiency. Urines from patients were examined at outset, after 30 days and after 60 days of treatment and the concentrations of SH-reactive metals, total protein, sulfate, sulfite, thiosulfate and thiocyanate were determined. The concentrations of metals in hair were also determined. **RESULTS:** At the beginning of the study thiamine deficiency was observed in 3 out of the 10 patients. Out of 10 patients, 6 had initial urine samples containing arsenic in greater concentration than healthy controls. Traces of mercury were seen in urines from all of these autistic children. Following administration of TFD an increase in cadmium was seen in 2 children and in lead in one child. Nickel was increased in the urine of one patient during treatment. Sulfur metabolites in urine did not differ from those measured in healthy children. **CONCLUSIONS:** Thiamine tetrahydrofurfuryl disulfide appears to have a beneficial clinical effect on some autistic children, since 8 of the 10 children improved clinically. We obtained evidence of an association of this increasingly occurring disease with presence of urinary SH-reactive metals, arsenic in particular.

4.1.22. Rugino, T.A., Samscock, T.C. "Levetiracetam in autistic children: an open-label study." *J Dev Behav Pediatr* 2002 Aug;23(4):225-30. Publication Types: Clinical Trial.

Department of Pediatrics, Marshall University Joan C Edwards School of Medicine, Huntington, West Virginia, USA. drtomrug@mac.com

The objectives of this study were to determine whether autistic children taking levetiracetam (1) showed improvement in the areas of aggression, impulsivity, hyperkinesis, and mood instability, and (2) showed a nootropic response. Ten white autistic boys ranging from 4 to 10 years were compared pretreatment and while taking levetiracetam for an average of 4.1 weeks. Inattention, hyperkinesis, and impulsivity were evaluated using the Achenbach Attention Problems scale, Conners DSM-IV Total scale, and the Conners Attention-Deficit Hyperactivity Disorder Index scale, all of which showed statistically significant improvements. Mood instability was measured with the Conners Global Index (CGI)

Emotional Lability and CGI Total scales, both of which showed statistically significant improvements. Aggressive behavior, as measured with the Achenbach Aggression scale, showed statistically significant improvement only for subjects who were not recently weaned from medications that reduce aggression (e.g., risperidone, carbamazepine, desipramine). Levetiracetam may reduce hyperactivity, impulsivity, mood instability, and aggression in autistic children with these problems. No nootropic effect was observed.

4.1.23. McDougle, C.J., Kem, D.L., Posey, D.J. "Case series: use of ziprasidone for maladaptive symptoms in youths with autism." *J Am Acad Child Adolesc Psychiatry* 2002 Aug;41(8):921-7.

Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202-4800, USA.

OBJECTIVE: To conduct a preliminary evaluation of the safety and effectiveness of ziprasidone in children, adolescents, and young adults with autism. **METHOD:** Twelve patients (mean age +/- SD, 11.62 +/- 4.38 years; range, 8-20 years) with DSM-IV-defined autism (n = 9) or pervasive developmental disorder not otherwise specified (n = 3) received open-label treatment with ziprasidone (mean daily dose, 59.23 +/- 34.76 mg; range, 20-120 mg) for at least 6 weeks (mean duration, 14.15 +/- 8.29 weeks; range, 6-30 weeks). **RESULTS:** Six (50%) of the 12 patients were considered responders based on a Clinical Global Impression Scale rating of "much improved" or "very much improved." Transient sedation was the most common side effect. No cardiovascular side effects, including chest pain, tachycardia, palpitations, dizziness, or syncope, were observed or reported. The mean change in body weight for the group was -5.83 +/- 12.52 lb (range, -35 to +6 lb). Five patients lost weight, five had no change, one gained weight, and one had no follow-up weight obtained beyond the baseline measurement. **CONCLUSIONS:** Ziprasidone appears to have the potential for improving symptoms of aggression, agitation, and irritability in children, adolescents, and young adults with autism. Significant weight gain was not observed in this short-term trial. Double-blind, placebo-controlled studies are needed to substantiate these preliminary findings.

4.1.24. Cohen, B.I. "Use of a GABA-transaminase agonist for treatment of infantile autism." *Med Hypotheses* 2002 Jul;59(1):115-6.

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This paper describes the use of a GABA-transaminase agonist for the treatment of infantile autism. An approximate one third reduction of GABA and ammonia levels for an autistic patient with noticeable improvement of verbal/language skills and a reduction of repetitious ritualistic self-stimulatory behavior (stimming) was observed. A reduction of the plasma GABA (by administering a GABA-T agonist, Imipramine) probably results in more axon(s)-to-oligodendrocyte signaling in the corpus callosum and it is postulated that this could result in a reduction of the autistic features for the patient.

4.1.25. McCracken, J.T., McGough, J., Shah, B., Cronin, P., Hong, D., Aman, M.G., Arnold, L.E., Lindsay, R., Nash, P., Hollway, J., McDougle, C.J., Posey, D., Swiezy, N., Kohn, A., Scabill, L., Martin, A., Koenig, K., Volkmar, F., Carroll, D., Lancor, A., Tierney, E., Ghuman, J., Gonzalez, N.M., Grados, M., Vitiello, B., Ritz, L., Davies, M., Robinson, J., McMahon, D.; Research Units on Pediatric Psychopharmacology Autism Network. "Risperidone in children with autism and serious behavioral problems." *N Engl J Med* 2002 Aug 1;347(5):314-21. Publication Types: Clinical Trial, Multicenter Study, Randomized Controlled Trial.

University of California, Los Angeles, USA.

BACKGROUND: Atypical antipsychotic agents, which block postsynaptic dopamine and serotonin receptors, have advantages over traditional antipsychotic medications in the treatment of adults with schizophrenia and may be beneficial in children with autistic disorder who have serious behavioral disturbances. However, data on the safety and efficacy of atypical antipsychotic agents in children are limited. **METHODS:** We conducted a multisite, randomized, double-blind trial of risperidone as compared with placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in children 5 to 17 years old. The primary outcome measures were the score on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions - Improvement (CGI-I) scale at eight weeks. **RESULTS:** A total of 101 children (82 boys and 19 girls; mean [+/-SD] age, 8.8+/-2.7 years) were randomly assigned to receive risperidone (49 children) or placebo (52). Treatment with risperidone for eight weeks (dose range, 0.5 to 3.5 mg per day) resulted in a 56.9 percent reduction in the Irritability score, as compared with a 14.1 percent decrease in the placebo group (P<0.001). The rate of a positive response, defined as at least a 25 percent decrease in the Irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69 percent in the risperidone group (34 of 49 children had a positive response) and 12 percent in the placebo group (6 of 52, P<0.001). Risperidone therapy was associated with an average weight gain of 2.7+/-2.9 kg, as compared with 0.8+/-2.2 kg with placebo (P<0.001). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group (P<0.05 for each comparison). In two thirds of the children with a positive response to risperidone at eight weeks (23 of 34), the benefit was maintained at six months. **CONCLUSIONS:** Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. The short period of this trial limits inferences about adverse effects such as tardive dyskinesia. Copyright 2002 Massachusetts Medical Society

4.1.26. Nieoullon, A. "Dopamine and the regulation of cognition and attention." *Prog Neurobiol* 2002 May;67(1):53-83. Publication Types: Review, Review, Academic.

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Dopamine (DA) acts as a key neurotransmitter in the brain. Numerous studies have shown its regulatory role for motor and limbic functions. However, in the early stages of Parkinson's disease (PD), alterations of executive functions also suggest a role for DA in regulating cognitive functions. Some other diseases, which can also involve DA dysfunction, such as schizophrenia or attention deficit hyperactivity disorder (ADHD) in children, as shown from the ameliorative action of dopaminergic antagonists and agonists, respectively, also show alteration of cognitive functions. Experimental studies showed that selective lesions of the dopaminergic neurons in rats or primates can actually provide cognitive deficits, especially when the mesocorticolimbic component of the dopaminergic systems is altered. Data from the experiments also showed significant alteration in attentional processes, thus raising the question of direct involvement of DA in regulating attention. Since the dopaminergic influence is mainly exerted over the frontal lobe and basal ganglia, it has been suggested that cognitive deficits express alteration in these subcortical brain structures closely linked to cortical areas, more than simple deficit in dopaminergic transmission. This point is still a matter of debate but, undoubtedly, DA acts as a powerful regulator of different aspects of cognitive brain functions. In this respect, normalizing DA transmission will contribute to improve the cognitive deficits not only related to neurologic or psychiatric diseases, but also in normal aging. Ontogenic and phylogenetic analysis of dopaminergic systems can provide evidences for a role of DA in the development of cognitive general capacities. DA can have a trophic action during maturation, which may influence the later cortical specification, particularly of pre-frontal cortical areas. Moreover, the characteristic extension of the dopaminergic cortical innervation in the rostro-caudal direction during the last stages of evolution in mammals can also be related to the appearance of progressively more developed cognitive capacities. Such an extension of cortical DA innervation could be related to increased processing of cortical information through basal ganglia, either during the course of evolution or development. DA has thus to be considered as a key neuroregulator which contributes to behavioral adaptation and to anticipatory processes necessary for preparing voluntary action consequent upon intention. All together, it can be suggested that a correlation exists between DA innervation and expression of cognitive capacities. Altering the dopaminergic transmission could, therefore, contribute to cognitive impairment. Copyright 2002 Elsevier Science Ltd.

4.1.27. Patel, N.C., Yeh, J.Y., Shepherd, M.D., Crismon, M.L. "Secretin treatment for autistic disorder: a critical analysis." *Pharmacotherapy* 2002 Jul;22(7):905-14. Publication Types: Review, Review, Multicase.

College of Pharmacy, The University of Texas at Austin, Austin State Hospital, Texas Department of Mental Health and Retardation, 78712, USA.

We assessed evidence of the effects of secretin on behavior in individuals with autistic disorder. Articles were obtained through a MEDLINE search of the English-language literature

from January 1966-November 2001; all investigations and case reports on the topic were included. Press releases obtained from the World Wide Web also were included. Secretin, a gastrointestinal hormone, is suggested to improve autistic symptoms, particularly social function and communication. Two formulations, porcine and synthetic human secretin, were evaluated in humans. A small body of literature and popular belief in autistic disorder communities supported the agent's efficacy. A number of controlled clinical trials did not show improvement in autistic symptoms with secretin compared with placebo, possibly indicating no role for the drug in autistic disorder.

4.1.28. Sponheim, E., Oftedal, G., Helverschou, S.B. "Multiple doses of secretin in the treatment of autism: a controlled study." *Acta Paediatr* 2002;91(5):540-5. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Dramatic effects on autistic behaviour after repeated injections of the gastrointestinal hormone secretin have been referred in a number of case reports. In the absence of curative and effective treatments for this disabling condition, this information has created new hope among parents. Although controlled studies on the effect of mainly one single dose have not documented any effect, many children still continue to receive secretin. Six children enrolled in a double-blind, placebo-controlled crossover study in which each child was its own control. Human synthetic secretin, mean dose 3.4 clinical units, and placebo were administered intravenously in randomized order every 4th wk, on three occasions each. The measurement instruments were the visual analogue scale (VAS) and the aberrant behaviour checklist (ABC). Statistically significant differences were found for placebo in 3 out of 6 children and for secretin in one child, using parental ratings only (VAS scores). Differences were small and lacked clinical significance, which was in accordance with the overall impression of the parents and teachers and visual inspection of graphs. Conclusion: In this placebo-controlled study, multiple doses of secretin did not produce any symptomatic improvement.

4.1.29. Carey, T., Ratliff-Schaub, K., Funk, J., Weinle, C., Myers, M., Jenks, J. "Double-blind placebo-controlled trial of secretin: effects on aberrant behavior in children with autism." *J Autism Dev Disord* 2002 Jun;32(3):161-7. Publication Types: Clinical Trial, Evaluation Studies, Randomized Controlled Trial.

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Secretin has been proposed as a treatment alternative for autistic spectrum disorders, but empirical support is lacking. A double-blind placebo-controlled study examined the effect of a single dose of synthetic human secretin on aberrant behavior. Parent and teacher data from the Aberrant Behavior Checklist for eight male children were analyzed for reliable change in a clinical replication series. By parent and teacher

report, the majority of change occurred either on the placebo trial or reflected deterioration subsequent to secretin infusion. Repeated-measures multivariate analysis of variance results were similar. Results are consistent with other studies, suggesting that secretin may not be an effective treatment option.

4.1.30. Kern, J.K., Van Miller, S., Evans, P.A., Trivedi, M.H. "Efficacy of porcine secretin in children with autism and pervasive developmental disorder." *J Autism Dev Disord* 2002 Jun;32(3):153-60. Publication Types: Clinical Trial. Randomized Controlled Trial.

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Secretin, a gastrointestinal (GI) hormone, was reported in a preliminary study to improve language and behavior in children with autism/pervasive developmental disorder (PDD) and chronic diarrhea. To determine the efficacy of secretin, we completed a double-blind, placebo-controlled, crossover (3 weeks) study in children with autism/PDD and various GI conditions using a single dose of intravenous porcine secretin. Children with chronic, active diarrhea showed a reduction in aberrant behaviors when treated with the secretin but not when treated with the placebo. Children with no GI problems are unaffected by either secretin or placebo. The improvement seen with secretin in children with autism/PDD and chronic diarrhea suggests that there may be a subtype of children with autism/PDD who respond to secretin.

4.1.31. Edwards, R.J., Pople, I.K. "Side-effects of risperidone therapy mimicking cerebrospinal fluid shunt malfunction: implications for clinical monitoring and management." *J Psychopharmacol* 2002 Jun;16(2):177-9.

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Risperidone is an atypical antipsychotic used in the treatment of several psychiatric disorders in both children and adults. We present two patients with hydrocephalus and learning difficulties who were admitted to the neurosurgical unit with a suspected cerebrospinal fluid shunt malfunction and raised intracranial pressure. They had both been commenced on risperidone for the treatment of aggressive outbursts. Twelve days after commencing risperidone, the first patient developed symptoms of headache, nausea, vomiting, drowsiness, lethargy and two episodes of collapse. The second patient presented with similar symptoms 4 days after his risperidone dose was increased. An unnecessary shunt exploration was averted in both cases when it was noted that the side-effect profile of risperidone mimicked exactly those of shunt malfunction. Discontinuation of the drug resulted in complete resolution of all symptoms within 72 h. Many patients with shunted hydrocephalus have associated developmental disorders that may warrant treatment with risperidone. Clinicians should be aware of the potential symptom overlap between shunt malfunction and risperidone side-effects in these patients.

4.1.32. Brudnak, M.A., Rimland, B., Kerry, R.E., Dailey, M., Taylor, R., Stayton, B., Waickman, F., Waickman, M., Pangborn, J., Buchholz, I. "Enzyme-based therapy for autism spectrum disorders — is it worth another look?" *Med Hypotheses* 2002 May;58(5):422-8. Publication Types: Clinical Trial.

Autism Research Institute, San Diego, CA, USA.

Autism is a developmental disease usually manifesting within the first three years of life. To date, no causative agent has been found. Similarly, treatment options have been limited. Of the treatment options available, a number of them have been nutritionally based in an attempt to address one or more of the theories regarding the etiology of the disease. An example would be enzyme therapy for the digestion of purported offending neuroactive peptides collectively known as exorphins. This paper discusses the exorphin theory of autism and subsequent treatment with dietary enzyme therapy. Novel data are presented in support of the theory that enzymes play a critical role in autism. Forty-six patients between the ages of 5 and 31 were selected for inclusion in the study based on a diagnosis placing them in the category of the autism spectrum disorders (ASD). The diets were supplemented with a novel dietary enzyme formulation, ENZYMAID, for a period of 12 weeks. Progress was tracked according to the Symptom Outcome Survey (SOS) (1) form method of symptom charting and presented in a table for further analysis. The novel enzyme formula, ENZYMAID, beneficially and safely affected all 13 of the parameters measured. Improvements ranged from 50-90%, depending on the parameter measured. Enzyme therapy to treat ASD may indeed be a viable option in treatment protocols. These results indicate that further controlled studies are warranted. Copyright 2002 Published by Elsevier Science Ltd.

4.1.33. Brudnak, M.A. "Probiotics as an adjuvant to detoxification protocols." *Med Hypotheses* 2002 May;58(5):382-5. Publication Types: Review, Review, Tutorial.

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Autism is a developmental disease characterized by a spectrum of symptoms ranging from decreased verbal skills and social withdrawal, to repetitive behavior and violent outbursts. Genetic analysis has yielded a few potentially interesting genes, however no clear linkage has been established. For this reason, it has been suggested that the etiology of autism may involve multiple loci. This, in large part, explains why so many different theories abound. One such theory is that of mercury poisoning. Environmentally acquired mercury, either through some causal contact or through vaccination, has been postulated as the culprit. Mercury is thought to be exerting its neurological effect on the brain. The standard treatment has been to apply chelating agents in an attempt to extricate the mercury. One missing component in the treatment is the utilization of the body's own detoxification mechanisms. Arguably the largest detoxification component of the body, the endogenous enteric bacteria are an enormous reservoir, which can be constantly

and safely replenished. This paper discusses the use of high-dose probiotics as an adjuvant for detoxification protocols with an emphasis on use in autistics. Copyright 2002 Published by Elsevier Science Ltd.

4.1.34. Slassi, A. "Recent advances in 5-HT_{1B/1D} receptor antagonists and agonists and their potential therapeutic applications." *Curr Top Med Chem* 2002 Jun;2(6):559-74. Publication Types: Review Review Literature.

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The human 5-HT_{1B} and 5-HT_{1D} receptors are especially similar in sequence despite being encoded by two distinct genes. Although, human 5-HT_{1B} and 5-HT_{1D} receptors have been pharmacologically differentiated using nonselective 5-HT_{1B/D} receptor antagonists such as ketanserin (1), ritanserin (2) and methiothepin (3), the precise function of these receptors remains undefined, and progress toward this has been hampered by the lack of selective ligands. The interest of the major pharmaceutical companies in 5-HT_{1B/1D} antagonists increased by the discovery of potent and selective tools, combined with the fact that the blockade of terminal 5-HT_{1B} receptors by selective antagonists has been proposed as a new approach for more efficient and/or fast-acting antidepressant drugs, since the acute blockade of these 5-HT autoreceptors will, in theory, immediately mimic their desensitization. Furthermore, it has been also suggested that supersensitive 5-HT_{1B/1D} receptors may be involved in the pathophysiology of obsessive compulsive disorders (OCD). In the 5-HT_{1B/1D} agonist field, since the discovery of sumatriptan (26) (a 5-HT_{1B/1D} receptor agonist) as an effective treatment for migraine headache, intensive research in this area has led to several second-generation compounds, a few of which have either entered the market place or are in late clinical trials. Beside the antimigraine activity of the 5-HT_{1B/1D} agonists in clinical evaluation or already on the market, other potential therapeutic evaluations (such as gastric motor effect, bipolar disorder, autism, anti-aggressive effects) with these drugs are being investigated. This article highlights and reviews the research advances published in the 5-HT_{1B/1D} antagonist and agonist literature. The article is supplemented with selected references on the design, synthesis and development of novel 5-HT_{1B/1D} agents, and on studies to understand their mechanism and pathophysiology. Emphasis is given to recent advances in the potential therapeutic applications of 5-HT_{1B/1D} serotonergic agents. By no means has any attempt been made to exhaustively review the literature but rather, primary references along with citations to recent literature reviews have been included in each section.

4.1.35. Piyasirisilp, S., Hemachudha, T. "Neurological adverse events associated with vaccination." *Curr Opin Neurol* 2002 Jun;15(3):333-8. Publication Types: Review, Review, Tutorial.

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Public tolerance to adverse reactions is minimal. Several reporting systems have been established to monitor adverse events following immunization. The present review summarizes data on neurologic complications following vaccination, and provides evidence that indicates whether they were directly associated with the vaccines. These complications include autism (measles vaccine), multiple sclerosis (hepatitis B vaccine), meningoencephalitis (Japanese encephalitis vaccine), Guillain-Barre syndrome and giant cell arteritis (influenza vaccine), and reactions after exposure to animal rabies vaccine. Seizures and hypotonic/hypo-responsive episodes following pertussis vaccination and potential risks associated with varicella vaccination, as well as vaccine-associated paralytic poliomyelitis following oral poliovirus vaccination, are also described. In addition, claims that complications are caused by adjuvants, preservatives and contaminants [i.e. macrophagic myofasciitis (aluminium), neurotoxicity (thimerosal), and new variant Creutzfeldt-Jakob disease (bovine-derived materials)] are discussed.

4.1.36. Strauss, W.L., Unis, A.S., Cowan, C., Dawson, G., Dager, S.R. "Fluorine magnetic resonance spectroscopy measurement of brain fluvoxamine and fluoxetine in pediatric patients treated for pervasive developmental disorders." *Am J Psychiatry* 2002 May;159(5):755-60.

Center on Human Development and Disability, University of Washington, Seattle, 98105-6099, USA.

OBJECTIVE: Pediatric populations, including those with autistic disorder or other pervasive developmental disorders, increasingly are being prescribed selective serotonin reuptake inhibitors (SSRIs). Little is known about the age-related brain pharmacokinetics of SSRIs; there is a lack of data regarding optimal dosing of medications for children. The authors used fluorine magnetic resonance spectroscopy (¹⁹F MRS) to evaluate age effects on whole-brain concentrations of fluvoxamine and fluoxetine in children taking SSRIs. **METHOD:** Twenty-one pediatric subjects with diagnoses of autistic disorder or other pervasive developmental disorders, 6-15 years old and stabilized with a consistent dose of fluvoxamine or fluoxetine, were recruited for the study; 16 successfully completed the imaging protocol. Whole-brain drug levels in this group were compared to similarly acquired data from 28 adults. **RESULTS:** A significant relationship between dose and brain drug concentration was observed for both drugs across the age range studied. Brain fluvoxamine concentration in the children was lower, consistent with a lower dose/body mass drug prescription; when brain concentration was adjusted for dose/mass, age effects were no longer significant. Brain fluoxetine concentration was similar between age groups; no significant age effects on brain fluoxetine drug levels remained after adjustment for dose/mass. Observations of brain fluoxetine bioavailability and elimination half-life also were similar between age groups. **CONCLUSIONS:** These findings suggest that fluvoxamine or fluoxetine prescriptions adjusted for dose/mass are an acceptable treatment approach for medicating children with autistic disorder or other pervasive developmental disorders. It must be determined whether these findings can be generalized to other pediatric populations.

4.1.37. Barnard, L., Young, A.H., Pearson, J., Geddes, J., O'Brien, G. "A systematic review of the use of atypical antipsychotics in autism." *J Psychopharmacol* 2002 Mar;16(1):93-101. Publication Types: Review, Review, Tutorial.

Developmental Psychiatry Research Unit, School of Neuroscience and Psychiatry, University of Newcastle, Newcastle upon Tyne, UK.

Conventional antipsychotic medication is commonly prescribed to patients with autistic spectrum disorder. However, a high incidence of severe adverse reactions highlights the need to find more favourable treatments. Atypical antipsychotics may combine efficacy in ameliorating some autistic symptoms with a lower incidence of some adverse reactions. This article reviews the use of atypical antipsychotics in autistic disorder, with particular focus on behaviour, cognition and physical well-being. Thirteen studies using risperidone, three using olanzapine, one using clozapine, one using amisulpride and one using quetiapine were identified. Few firm conclusions can be drawn due to the limitations of the studies; however, there is an indication that risperidone may be effective in reducing hyperactivity, aggression and repetitive behaviours, often without inducing severe adverse reactions. Olanzapine and clozapine may also be effective; however, there is little evidence for using amisulpride or quetiapine in this population. Randomized trials are required to clarify the effectiveness of these agents.

4.1.38. Latif, A., Heinz, P., Cook, R. "Iron deficiency in autism and Asperger syndrome." *Autism* 2002 Mar;6(1):103-14.

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This research considers the prevalence of iron deficiency in children with autism and Asperger syndrome and examines whether this will influence guidelines and treatment. Retrospective analysis of the full blood count and, as far as available, serum ferritin measurements of 96 children (52 with autism and 44 with Asperger syndrome) was undertaken. Six of the autistic group were shown to have iron deficiency anaemia and, of the 23 autistic children who had serum ferritin measured, 12 were iron deficient. Only two of the Asperger group had iron deficiency anaemia and, of the 22 children who had their serum ferritin measured, only three were iron deficient. Iron deficiency, with or without anaemia, can impair cognition and affect and is associated with developmental slowing in infants and mood changes and poor concentration in children. This study showed a very high prevalence of iron deficiency in children with autism, which could potentially compromise further their communication and behavioural impairments.

4.1.39. Malone, R.P., Maislin, G., Choudhury, M.S., Gifford, C., Delaney, M.A. "Risperidone treatment in children and adolescents with autism: short- and long-term safety and effectiveness." *J Am Acad Child Adolesc Psychiatry* 2002 Feb;41(2):140-7. Publication Types: Clinical Trial.

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OBJECTIVE: Atypical neuroleptics, including risperidone, are used to treat children with autism, despite limited efficacy and safety data. Many clinicians believe that risperidone will not induce dyskinesias in children. The authors investigated open risperidone treatment in children with autism and included findings on dyskinesias. **METHOD:** The sample included 22 outpatients (mean age = 7.1 years) diagnosed with autism (DSM-IV). Treatment consisted of a 1-month short-term phase followed by a 6-month long-term phase. At the end of the long-term phase, drug was discontinued, and the need for further drug treatment and the occurrence of withdrawal dyskinesias were assessed. Measures included the Clinical Global Impressions (CGI), Children's Psychiatric Rating Scale (CPRS), and the Abnormal Involuntary Movement Scale. **RESULTS:** The mean risperidone dosage was 1.2 mg/day. Overall, the children had significant clinical improvement as assessed by the CPRS and CGI. Untoward effects included sedation, increased appetite, and weight gain. Two of 13 (15.4%) children treated long-term developed mild, reversible withdrawal dyskinesias when risperidone was discontinued. No child developed dyskinesias on risperidone. **CONCLUSIONS:** Risperidone shows promise as a treatment in autism. However, withdrawal dyskinesias were noted. Further assessment of the risk of risperidone-related dyskinesias is indicated.

4.1.40. Page, T., Moseley, C. "Metabolic treatment of hyperuricosuric autism." *Prog Neuropsychopharmacol Biol Psychiatry* 2002 Feb;26(2):397-400.

Department of Neurosciences, University of California, San Diego, La Jolla 92093-0624, USA.

A single male subject with hyperuricosuric autism was treated for a period of 2 years with an oral dose of uridine, which increased from 50 to 500 mg/kg/day. This patient experienced dramatic social, cognitive, language, and motor improvements. These improvements decreased within 72 h of the discontinuation of uridine, but reappeared when uridine supplementation was resumed. Thus, it appears that patients with hyperuricosuric autism benefit from metabolic therapy with oral uridine therapy in a manner similar to that seen in other disorders of purine metabolism in which there is autistic symptomatology.

4.1.41. Simeon, J., Milin, R., Walker, S. "A retrospective chart review of risperidone use in treatment-resistant children and adolescents with psychiatric disorders." *Prog Neuropsychopharmacol Biol Psychiatry* 2002 Feb;26(2):267-75. Publication Types: Review, Review, Multicase.

Royal Ottawa Hospital, Ontario, Canada.

Antipsychotic drugs are used to treat a wide variety of child psychiatric disorders characterized by psychotic symptoms, aggression, excitement, tics, stereotypies and hyperactivity nonresponsive to other therapies. Unfortunately, typical antipsychotics have many adverse effects limiting their long-

term use. Novel antipsychotics with combined dopaminergic and serotonergic action, such as risperidone, appear to offer better safety and efficacy profiles in controlled studies of adult patients, and therefore appeared as promising pharmacotherapeutic agents in child psychiatry. The purpose of this retrospective chart review was to obtain data on the potential effectiveness and tolerability of risperidone in children and adolescents presenting with a variety of chronic and severe psychiatric disorders who had been unresponsive to previous pharmacological treatments. Charts for 106 children and adolescents (males $n = 81$ or 76.4%; females $n = 25$ or 23.6%), presenting with attention deficit and/or hyperactivity disorder ($n = 49$ or 46.2%), conduct disorder ($n = 13$ or 12.3%), oppositional-defiant disorder ($n = 5$ or 4.7%), behavioural problems not otherwise specified ($n = 2$ or 1.9%), autism ($n = 8$ or 7.5%), Asperger's syndrome ($n = 8$ or 7.5%), pervasive developmental disorder (PDD) not otherwise specified ($n = 4$ or 3.8%), anxiety ($n = 6$ or 5.7%), depression ($n = 2$ or 1.9%), dysthymia ($n = 2$ or 1.9%), schizophrenia ($n = 4$ or 3.8%), adjustment disorder ($n = 1$ or 0.9%) and obsessive-compulsive disorder ($n = 2$ or 1.9%) were reviewed retrospectively to determine the tolerability and potential efficacy of risperidone treatment for a variety of psychiatric disorders. Six subjects also presented with mental retardation. The average length of illness prior to risperidone treatment was 5 years and the average age of risperidone treatment onset was 11 years. The mean daily dose of risperidone was 1.2 mg (range = 0.25 to 8.0 mg). Very few adverse effects were reported. The average length of risperidone treatment was 11 months with the majority ($n = 75$ or 76%) of patients maintained on risperidone following study termination. Seven cases (6.6%) were missing follow-up data. The majority ($n = 78$ or 74%) of patients were taking concurrent psychiatric medications, most commonly stimulants for the treatment of ADHD. Clinical global improvements for children and adolescents at the final study visit were marked ($n = 37$ or 34.9%), moderate ($n = 40$ or 37.7%), mild ($n = 13$ or 12.4%), none ($n = 12$ or 11.3%), or worse ($n = 1$ or 1%). Three cases (2.9%) were missing clinical improvement data. Results suggest that risperidone may be useful for managing behavioural disturbances and psychotic symptoms associated with a wide variety of childhood psychiatric disorders. For most patients in the study, a combination of risperidone and adjunctive pharmacotherapy was beneficial. Controlled and discontinuation studies of risperidone treatment in children and adolescents with behavioural and psychotic disorders are recommended.

4.1.42. Kaminska, B., Czaja, M., Kozielska, E., Mazur, E., Korzon, M. "Use of secretin in the treatment of childhood autism." *Med Sci Monit* 2002 Jan; 8(1): RA 22-6. Publication Types: Review, Tutorial.

Department and Clinic of Pediatrics, Gastroenterology and pediatric Oncology, Medical University, Gdansk, Poland.

The paper presents current views concerning childhood autism. The authors present the concepts of Etiology of this disorder, emphasizing the role of negative psychical stimuli in early childhood and the role of mother's contact with the

child. Organic factors, including genetic background, developmental abnormalities of the nervous system, teratogenic factors and perinatal traumas are also taken in to consideration. The role of metabolic factors and enterhormones, particularly those belonging to the secretin group and their effect on the function of the gastrointestinal tract and central nervous system is emphasized. We discuss signs which may be indicative of first symptoms of autism in different age groups. A typical symptom of autism is no development of speech, observed from infancy, taking the form of complete mutism at later stages. It has been emphasized that most pathologic symptoms result from altered perception of external stimuli, which arouse fear and anxiety. Autistic patients may suffer from gastrointestinal tract disturbances such as abdominal pains and diarrhea. Methods used hitherto in the therapy of childhood autism, mainly by psychologists and psychiatrists, as well as some attempts of pharmacological treatment, are presented. The structure and function of secretin, as well as its effects on the pancreas are discussed. The role of secretin in diagnostic tests, among others in the diagnosis of gastrinoma, is emphasized. We also present the history of the application of secretin in the therapy of childhood autism.

4.1.43. Scahill, L., McCracken, J., McDougle, C.J., Aman, M., Arnold, L.E., Tierney, E., Cronin, P., Davies, M., Ghuman, J., Gonzalez, N., Koenig, K., Lindsay, R., Martin, A., McGough, J., Posey, D.J., Swiezy, N., Volkmar, F., Ritz, L., Vitiello, B. "Methodological issues in designing a multisite trial of risperidone in children and adolescents with autism." *J Child Adolesc Psychopharmacol* 2001 Winter;11(4):377-88. Publication Types: Clinical Trial, Randomized Controlled Trial.

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OBJECTIVE: To describe the methodological challenges and decisions made in developing a multisite, controlled study of risperidone in children and adolescents with autism. **METHODS:** Review the design considerations for clinical trials in children with autistic disorder accompanied by severe tantrums, aggressive and/or self-injurious behaviors. These design considerations include the definition of inclusion criteria that are relevant to clinical practice and matching study design to the goal of evaluating short- and long-term effects. Additional ethical and scientific issues concern the length of trial and sample size. **RESULTS:** We undertook a short-term, placebo-controlled study to evaluate the efficacy and safety of risperidone in children and adolescents with autistic disorder. This trial design was followed by an extended open-label maintenance on risperidone to confirm durability of treatment effects and to monitor safety. Finally, a placebo-controlled discontinuation study tested the need for continuous treatment. **CONCLUSIONS:** In the absence of standard pharmacological treatment for children with autistic disorder, a placebo-controlled study remains the most appropriate method of testing efficacy and safety. The clinical relevance of this study is enhanced by the addition of an extended maintenance phase followed by a placebo discontinuation.

4.1.44. Tsang, R.W., Solow, H.L., Ananthanarayan, C., Haley, S. "Daily general anaesthesia for radiotherapy in unco-operative patients: ingredients for successful management." *Clin Oncol (R Coll Radiol)* 2001;13(6):416-21. Publication Types: Review, Review of Reported Cases.

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An unco-operative patient requiring daily radiation therapy presents a difficult clinical problem. After reviewing the paediatric oncology literature addressing the use of general anaesthesia for short medical procedures, we have developed checklists of procedural guidelines and monitoring equipment for the safe use of daily anaesthesia in adult patients who require a fractionated course of radiation therapy. We illustrate this by describing the successful treatment of a woman with autism and Hodgkin's disease who required daily general anaesthesia for immobilization during a 4-week course of radiation therapy. Propofol was used as the primary drug and was not associated with any adverse side-effects. There was no development of tolerance.

4.1.45. Kauffmann, C., Vance, H., Pumariega, A.J., Miller, B. "Fluvoxamine treatment of a child with severe PDD: a single case study." *Psychiatry* 2001 Fall; 64(3): 268-77.

Department of Psychiatry and Behavioral Sciences, James H. Quillen College of medicine, East Tennessee State University, Johnson City, USA.

Recent reports suggest that selective serotonin reuptake inhibitors (SSRIs) are useful treatment of individuals with autism and other pervasive developmental disorders. We report on a single case study of the use of fluvoxamine with a 7-year-old Caucasian girl with severe pervasive developmental disorder. Our findings indicate that fluvoxamine was significantly effective in reducing stereotypical, repetitive behaviors, anxiety, and aggression and in improving preguistic and social behaviors. Our results indicate that the use of the SSRIs as a platform for the long-term abhikitation of these children should be considered, but further studies are required to establish the efficiency of fluvoxamine for the treatment of children with autism.

4.1.46. Owley, T., Mc Mahon, W., Cook, E.H., Laulhere, T., South, M., Mays, L.Z., Shernoff, E.S., Lainhart, J., Modahl, C.B., Corsello, C., Ozonoff, S., Risi, S., Lord, C., Leventhal, B.L., Filipek, P.A. "Multisite, double-blind, placebo-controlled trial of porcine secretin in autism." *J Am Acad Child Adolesc Psychiatry* 2001, Nov;40(11): 1293-9. Publication Types: Clinical Trial, Multicentre Study, Randomized Controlled Trial.

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OBJECTIVE: To examine the efficacy of intravenous porcine secretin for the treatment of autistic disorder. **METHOD:** Randomized, double-blind, placebo-controlled, crossover design. Fifty-six subjects with autistic disorder received either secretin or placebo infusion at baseline and the other

substance at week 4. Subjects were given the Autism Diagnostic Observation Schedule (ADOS) and other pertinent developmental measures at baseline and at weeks 4 and 8 to assess drug effects. **RESULTS:** For the primary efficacy analysis, change of ADOS social-communication total score from week 0 to week 4, no statistically significant differences were obtained between placebo (-0.6 +/- 1.4; t 54=0.346, p<.73). The other measures showed no treatment effect for secretin compared with placebo. **CONCLUSION:** There was no evidence for efficacy of secretin in this randomized, placebo-controlled, double-blind trial.

4.1.47. Lightdale, J.R., Hayer, C., Duer, A., Lind-White, C., Jenkins, S., Siegel, B., Elliott, G.R., Heyman, M.B. "Effects of intravenous secretin on language and behaviour of children with autism and gastrointestinal symptoms: a single-blinded, open-label pilot study." *Pediatrics* 2001 Nov; 108(5): E90.

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BACKGROUND: Autism is a severe developmental disorder with poorly understood etiology. A recently published case series describes 3 autistic children with gastrointestinal symptoms who underwent endoscopy and intravenous administration of secretin and were subsequently noted by their parents to demonstrate improved language skills over a 5-week period. This report sparked tremendous public interest, and investigators at several sites moved quickly to design controlled trials to test the efficacy of secretin as a therapy for autistic children. However, this is the first effort specially design to replicate the initial reported findings in terms of patient age, presenting symptoms, and drug administration. **OBJECTIVE:** To rigorously apply the scientific method by assessing the reproducibility of the reported effects of intravenous secretin on the language of young children with autism and gastrointestinal symptoms. **METHODS:** We performed a single-blinded, prospective, open-label trial by conducting formal language testing and blinded behavioural rating both before and repeatedly after a standardized infusion of secretin. We selected autistic children who were similar in age and profile to those described in the published retrospective case review. Inclusion criteria for study participation included age (3-6 years), confirmed diagnosis of autism, and reported gastrointestinal symptoms (16 had chronic diarrhea, 2 had gastroesophageal reflux, and 2 had chronic constipation). Twenty children (18 male) were admitted to the Pediatric Clinical Research Centre at the University of California, San Francisco after administration of the Preschool Language Scale-3 (PLS-3). A 3 CU/kg dose of secretin (Secretin - Ferring) was administered intravenously (upper endoscopy was not performed). Behavioral ratings were derived using the Autism Observation Scale applied to a 30-minute time sample of the child's behavior consisting of a videotape of the PLS-3 (structured setting) and second free play session with a standard set of developmentally appropriate toys. Participants then returned for follow-up evaluations, with readministrations of the PLS-3 at 1, 2, 3, and

5 weeks' postinfusion, and videotaping for each session for later blinded review by 2 independent observers using the Autism Observation Scale, uninformed about their impressions of the effects of secretin using a 5-point Likert scale for parents to rate changes seen in their child. RESULTS: With a total study completion rate across all participants of 96%, repeated measures analyses of variance revealed no significant increases in children's language skills from baseline across all 5 study time periods after a single infusion of secretin. Similarly, neither significant decreases in typical behaviors nor increases in prosocial behaviors and developmentally appropriate play skills emerged. Furthermore, no relationship was found between parental reports of change and observable improvement in the sample. Despite the objective lack of drug effect, 70% of parents in our study reported moderate to high change in their child's language and behavior. Furthermore, 85% of parents reported that they felt that their child would obtain at least some additional benefits from another infusion of secretin. CONCLUSIONS: The results of our pilot study indicate that interavenous secretin had no effects in a 5-week period on the language and behavior of 20 children our study with blinded reviews of patients both before and after secretin administration follows the scientific method by seeking to reproduce an observed phenomenon using validating and reliable outcome measures. Pilot studies remain a mandatory step for the design of future randomized, clinical trials investigating potential treatments for children with autism.

4.1.48. Hellings, J.A., Zarcone, J.R., Crandall, K., Wallace, D., Schroeder, S.R. "Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism." *J Child Adolesc Psychopharmacol* 2001 Fall; 11(3): 229-38. Publication Types: Clinical Trial, Controlled Clinical Trial.

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As a part of an ongoing, prospective, ABA design, double-blind crossover study of risperidone versus placebo for the treatment of aggressive, destructive and self-injurious behavior in persons aged 6-65 years with mental retardation (MR) and autism, we measured the weight of 19 subjects at each study visit. We compared mean weight gain during the 16-week acute phase and 24-week open maintenance phase with that during the 16-week acute phase and 24-week open maintenance phase with that during the initial and middle placebo phases statically, using a linear mixed model procedure. Results of the linear mixed model analysis showed that relative weight gain observed during the acute and maintenance drug phases was significantly greater than that observed during the initial and middle placebo phases respectively ($p=.0001$ and $p=.0001$). Over approximately a year children aged 8-12 ($n=5$) gained a mean of 8.2 kg (range = 2.7-17.7 kg) adolescents ($n=6$) aged 13-16 gained a mean of 8.4kg (range 3.6-15.5kg); adults aged 21-51 ($n=8$) gained a mean of 5.4kg (range 0-9.5 kg). Weight gain observed in this controlled study of risperidone treatment in children, adolescents and

adults with MR and autism was significant. It may be greater in this population than in others reported and in this study was not limited to an acute effect only. Rate of weight gain diminished rapidly on tapering and stopping the drug. Further studies are urgently needed, including those incorporating diet and exercise programming.

4.1.49. "Open trial of risperidone in 24 young children with pervasive developmental disorders." *J Am Acad Child Adolesc psychiatry* 2001 Oct;40(10): 1206-14. Publication Types: Clinical Trial.

METHOD : Twenty-four children aged 3.6 to 6.6 years (mean 4.6 years +/- 8 months) enrolled during 1999 and 2000 participated in a 16-week open-label trial with risperidone monotherapy. Outcome measures included the Children's Psychiatric Rating Scale (CPRS), Childhood Autism Rating Scale (CARS), Clinical Global Impression-Improvement (CGI-I) and Children's Global Assessment Scale (C-GAS). RESULTS: Two subjects did not complete the trial because of side effects. The optimal dose was 0.5 mg/day. After the treatment a 21% improvement in CPRS and a 14% improvement in CARS total scores was found. Items related to behavioral control (hyperactivity, fidgetiness, rhythmic motions) and affect regulation (lability of affect) improved more than 25%. Based on improvement of at least 25% on the CPRS and a score of 1 or 2 on the CGI-I, eight subjects were considered responders. Functional impairment (C-GAS) improved more than 25%. Thirteen subjects (54%) were free of any side effects; in the other participants risperidone was well tolerated. Only three subjects had a weight gain greater than 10%. CONCLUSIONS: Low-dose risperidone may positively affect symptoms in young autistic children, improving disruptive/hyperactive behavior and affective dysregulation. Further controlled studies in this age group are warranted.

4.1.50. Di Martino, A., Tuchman, R.F. "Antiepileptic drugs: affective use in autism spectrum disorders." *Pediatr Neurol* 2001 Sep; 25(3) : 199-207. Publication Types: Review, Review of Reported Cases, Tutorial.

Department of Neurosciences, University of Cagliari, Cagliari, Italy.

Antiepileptic drugs widely administered to individuals with autistic spectrum disorders. There are several reasons for the use of antiepileptic drugs in autistic spectrum disorders, including the high incidence of epilepsy in these individuals, the anecdotal reports suggesting an improvement of communication and behavior in autistic subjects with epileptic discharges, and the increased awareness that some disruptive behaviors may be manifestations of an associated affective disorder. In this study, data on the current use of antiepileptic drugs in the treatment of autism, and on the association of affective disorders with epilepsy and autism, are reviewed. The evidence supporting the hypothesis that there may be a subgroup of autistic children with epilepsy and affective disorders that preferentially respond to antiepileptic drugs is still very preliminary, and further investigations with double-blind controlled studies are needed. Although the role of

antileptic drugs at present time is not established, there is evidence that autism, epilepsy, and affective disorders commonly co-occur, and that they may share a common neurochemical substrate, which is the common target of the psychotropic mechanism of action of different antiepileptic drugs.

4.1.51. Malone, R.P., Cater, J., Sheikh, R.M., Choudhury, M.S., Delaney, M.A. "Olanzapine versus haloperidol in children with autistic disorder: an open pilot study." *J Am Acad Child Adolesc Psychiatry* 2001 Aug;40(8):887-94. Publication Types: Clinical Trial, Randomized Controlled Trial.

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OBJECTIVES: Conventional neuroleptics ameliorate symptoms in children with autistic disorder; however, they are known to cause dyskinesias. Atypical neuroleptics, including olanzapine, may have less risk for dyskinesia, but their efficacy in autistic disorder is not established. This study was designed to investigate the safety and effectiveness of open-label olanzapine as a treatment for children with autistic disorder by using haloperidol as a standard comparator treatment. **Method:** In a parallel groups design, 12 children with DSM-IV autistic disorder (mean age 7.8+/-2.1 years) were randomized to 6 weeks of open treatment with olanzapine or haloperidol. Mean final dosages were 7.9+/-2.5 mg/day for olanzapine and 1.4+/-0.7 mg/day for haloperidol. Outcome measures included the Clinical Global Impressions (CGI) and the Children's Psychiatric Rating Scale (CPRS). **RESULTS:** Both groups had symptom reduction. Five of six in the olanzapine group and three of six in the haloperidol group were rated as responders according to the CGI Improvement item. Subjects showed improvement on the CPRS Autism Factor ($F_{1,9} = 24.4$, $p = .0008$). Side effects included drowsiness and weight gain. **CONCLUSIONS:** The findings suggest that olanzapine is a promising treatment for children with autistic disorder. Further placebo-controlled and long-term studies of olanzapine in autistic disorder are required.

4.1.52. Morinushi, T., Ueda, Y., Tanaka, C. "Autistic children: experience and severity of dental caries between 1980 and 1995 in Kagoshima City, Japan." *J Clin Pediatr Dent* 2001 Summer;25(4):323-8.

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The present study indicates that experience and severity of dental caries in 1995 showed a clear decrease from observations in 1980 in Kagoshima City, Japan. This decline may be attributed to several factors such as the qualitative and quantitative improvements in treatment of caries, more regular visits to dental clinics, improved daily oral hygiene, and changes in dietary pattern.

4.1.53. Hollander, E., Dolgoff-Kaspar, R., Cartwright, C., Rawitt, R., Novotny, S. "An open trial of divalproex sodium in autism spectrum disorders." *J Clin Psychiatry* 2001 Jul;62(7):530-4. Publication Types: Clinical Trial.

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BACKGROUND: Autism spectrum disorders are characterized by core deficits in social interaction and speech/communication skills, repetitive behaviors, and restricted interests. Other abnormalities include seizures, electroencephalographic (EEG) abnormalities, affective instability, impulsivity, and aggression. Divalproex sodium is indicated as both an anticonvulsant in epilepsy and a mood stabilizer in bipolar illness and thus might be useful for these complicating symptoms in autism. **METHOD:** A retrospective pilot study was conducted to determine whether divalproex sodium was effective in treating core dimensions and associated features of autism. Fourteen patients who met DSM-IV criteria for autism, Asperger's disorder, or pervasive developmental disorder not otherwise specified, both with and without a history of seizure disorders or EEG abnormalities, were openly treated with divalproex sodium. Improvement was assessed via the Clinical Global Impressions-Improvement scale. **RESULTS:** Of 14 patients who completed a trial of divalproex sodium, 10 (71%) were rated as having sustained response to treatment. The mean dose of divalproex sodium was 768 mg/day (range, 125-2500 mg/day), and it was generally well tolerated. Improvement was noted in core symptoms of autism and associated features of affective instability, impulsivity, and aggression. **CONCLUSION:** Divalproex sodium may be beneficial to patients with autism spectrum disorders, particularly those with associated features of affective instability, impulsivity, and aggression as well as those with a history of EEG abnormalities or seizures. Of note, all patients with an abnormal EEG and/or seizure history were rated as responders. However, these findings must be interpreted with caution, given the open retrospective nature of the study. Controlled trials are needed to replicate these preliminary findings.

4.1.54. Surabian, S.R. "Developmental disabilities: epilepsy, cerebral palsy, and autism." *J Calif Dent Assoc* 2001 Jun;29(6):424-32. Publication Types: Review, Review, Tutorial.

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This article provides the dentist with a review of the three developmental disabilities that do not have mental retardation as a diagnostic component: epilepsy, cerebral palsy, and autism. Discussion focuses on diagnostic criteria and other dental and medical considerations. A greater understanding of developmental disabilities allows the dentist to offer care

in the dental office when feasible or to understand and develop referral relationships with colleagues who utilize the hospital operating room to provide comprehensive care.

4.1.55. Remington, G., Sloman, L., Konstantareas, M., Parker, K., Gow, R. "Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study." *J Clin Psychopharmacol* 2001 Aug;21(4):440-4. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Clomipramine, haloperidol, and placebo were compared with baseline in the treatment of autism, and overall outcome, specific symptoms, and side effects were examined. It was hypothesized that clomipramine would be better tolerated than haloperidol and prove superior on a measure of stereotypy. Individuals with a DSM-IV diagnosis of autistic disorder (mean age, 16.3 years; range, 10-36 years) were randomly assigned, by using a Latin square design, to the following 7-week trials: placebo, clomipramine (mean daily dose, 128.4 mg; range, 100-150 mg), or haloperidol (mean daily dose, 1.3 mg; range, 1-1.5 mg). Data on 36 subjects were analyzed and taken together; the results favored haloperidol. In those patients who were able to complete a full therapeutic trial, clomipramine proved comparable to haloperidol in terms of improvement compared with baseline. However, significantly fewer individuals receiving clomipramine versus haloperidol were able to complete the trial (37.5% vs. 69.7%, respectively) for reasons related to both side effects and efficacy or behavior problems. In the intent-to-treat sample, which is perhaps more clinically relevant, only haloperidol proved superior to baseline on a global measure of autistic symptom severity, as well as specific measures for irritability and hyperactivity. Clomipramine did not seem more effective on a measure of stereotypy, nor was it better tolerated.

4.1.56. Lindsay, L.A., Tsiouris, J.A., Cohen, I.L., Shindedecker, R., DeCresce, R. "Famotidine treatment of children with autistic spectrum disorders: pilot research using single subject research design." *J Neural Transm* 2001;108(5):593-611. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Using single subject research design, we performed pilot research to evaluate the safety and efficacy of famotidine for the treatment of children with autistic spectrum disorders. We studied 9 Caucasian boys, 3.8-8.1 years old, with a DSM-IV diagnosis of a pervasive developmental disorder, living with their families, receiving no chronic medications, and without significant gastrointestinal symptoms. The dose of oral famotidine was 2 mg/kg/day (given in two divided doses); the maximum total daily dose was 100 mg. Using single-subject research analysis and medication given in a randomized, double-blind, placebo-controlled, cross-over design, 4 of 9 children randomized (44%) had evidence of

behavioral improvement. Primary efficacy was based on data kept by primary caregivers, including a daily diary; daily visual analogue scales of affection, reciting, or aspects of social interaction; Aberrant Behavior Checklists (ABC, Aman); and Clinical Global Improvement scales. Children with marked stereotypy (meaningless, repetitive behaviors) did not respond. Our subjects did not have prominent gastrointestinal symptoms and endoscopy was not part of our protocol; thus, we cannot exclude the possibility that our subjects improved due to the effective treatment of asymptomatic esophagitis. The use of famotidine for the treatment of children with autistic spectrum disorders warrants further investigation.

4.1.57. Belsito, K.M., Law, P.A., Kirk, K.S., Landa, R.J., Zimmerman, A.W. "Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial." *J Autism Dev Disord* 2001 Apr;31(2):175-81. Publication Types: Clinical Trial, Randomized Controlled Trial.

The Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, Maryland, USA.

In autism, glutamate may be increased or its receptors up-regulated as part of an excitotoxic process that damages neural networks and subsequently contributes to behavioral and cognitive deficits seen in the disorder. This was a double-blind, placebo-controlled, parallel group study of lamotrigine, an agent that modulates glutamate release. Twenty-eight children (27 boys) ages 3 to 11 years (M=5.8) with a primary diagnosis of autistic disorder received either placebo or lamotrigine twice daily. In children on lamotrigine, the drug was titrated upward over 8 weeks to reach a mean maintenance dose of 5.0 mg/kg per day. This dose was then maintained for 4 weeks. Following maintenance evaluations, the drug was tapered down over 2 weeks. The trial ended with a 4-week drug-free period. Outcome measures included improvements in severity and behavioral features of autistic disorder (stereotypies, lethargy, irritability, hyperactivity, emotional reciprocity, sharing pleasures) and improvements in language and communication, socialization, and daily living skills noted after 12 weeks (the end of a 4-week maintenance phase). We did not find any significant differences in improvements between lamotrigine or placebo groups on the Autism Behavior Checklist, the Aberrant Behavior Checklist, the Vineland Adaptive Behavior scales, the PL-ADOS, or the CARS. Parent rating scales showed marked improvements, presumably due to expectations of benefits.

4.1.58. van der Walt, J.H., Moran, C. "An audit of perioperative management of autistic children." *Paediatr Anaesth* 2001 Jul;11(4):401-8.

Department of Paediatric Anaesthesia, Paediatric Day Surgery Unit, Women's and Children's Hospital, 72 King William Road, North Adelaide, South Australia 5006, Australia.

BACKGROUND: Autistic children are very difficult to manage in the hospital setting because they react badly to any change in routine. METHODS: We have developed a unique management program for autistic children admitted for medical and surgical procedures requiring a general

anaesthetic. Details of each patient managed according to this program have been prospectively entered into an Autistic Register. **RESULTS:** An audit of this database shows that we have administered anaesthesia on 87 occasions for 59 autistic children over 4 years. **CONCLUSIONS:** There is great variation in the severity of autism and hospital needs of these children. The focus is on early communication with the patient's families, flexibility to individualize the admission process and anaesthetic plan with admission and early discharge on the day of surgery whenever possible. Oral midazolam is an effective premedication for the milder cases and oral ketamine is the most reliable for moderate and severe cases. Comparison of oral midazolam and ketamine shows no significant different postoperative recovery and hospital discharge times. Routine intravenous fluids and antiemesis prophylaxis with removal of the i.v. cannula before return to the ward are also seen as important steps to decrease stress and smooth the postoperative phase. This program has also successfully been extended to the management of problem children due to other causes.

4.1.59. Masi, G., Cosenza, A., Mucci, M., De Vito, G. "Risperidone monotherapy in preschool children with pervasive developmental disorders." *J Child Neurol* 2001 Jun;16(6):395-400.

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The aim of this preliminary study was to examine the short-term efficacy and safety of the atypical antipsychotic risperidone in preschool autistic children. The sample consisted of 10 subjects (7 males and 3 females) aged 3 9/12 to 6 6/12 years (mean age 4.7 years). A 16-week open-label trial with risperidone monotherapy was initiated at a starting dose of 0.25 mg daily and was increased to a maximum dose of 0.50 mg (0.027 mg/kg daily). Outcome measures were the Childhood Autism Rating Scale, the Children's Psychiatric Rating Scale, Clinical Global Impression (improvement score), and the Children's Global Assessment of Functioning. Two subjects did not complete the trial because of side effects (tachycardia and flushes, fever and hyporexia). After the 16-week treatment, data from the eight children who completed the trial indicated a modest improvement in the Childhood Autism Rating Scale total score, Children's Psychiatric Rating Scale total score, and Children's Global Assessment of Functioning. According to the Clinical Global Impression, the global improvement score for four subjects was much improved or very much improved; the score for the other four children was minimally improved. None of the children exhibited behavioral deterioration. The side effects in the eight children were not severe.

4.1.60. Lamson, D.W., Plaza, S.M. "Transdermal secretin for autism - a case report." *Altern Med Rev* 2001 Jun;6(3):311-3.

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Secretin hormone given daily in transdermal cream was associated with marked and sustained developmental progress in an aphasic two-and-a-half year old child diagnosed with autism.

4.1.61. Santosh, P.J., Baird, G. "Pharmacotherapy of target symptoms in autistic spectrum disorders." *Indian J Pediatr* 2001 May;68(5):427-31.

Department of Child & Adolescent Psychiatry, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK. p.santosh@iop.kcl.ac.uk

There are no aetiologically-based treatments available to cure autism. Though psychotropics have a role in the management of some symptoms of autism, clinical trial evidence for the use of psychotropics is in its infancy and needs close monitoring. About half of the subjects with high functioning pervasive developmental disorders (PDDs) are currently reported to be on psychotropics (anti-depressants, stimulants and antipsychotics), with many of them being on anti-epileptic medication simultaneously. Despite this high level of psychotropic use, few studies exist investigating the pharmacokinetics, pharmacodynamics or side-effect profiles in this population. Multiprofessional and parent partnership is essential in managing autism and psychopharmacology should be used in conjunction with environmental manipulation, educational modification and/or behavioral management strategies. A symptomatic approach to managing the difficult behaviours associated with autism is recommended. Some symptoms of autism may be medication responsive (hyperactivity, obsessions, rituals, inattention, tics, etc), while other symptoms may be responsive to behavioural interventions, but may require medication (aggression, anxiety, depression, impulsivity, sleep difficulties, etc), and symptoms which need specific skill remediation are usually non-responsive to medication (deficits in academic, social or sport domains). The new atypical antipsychotics (such as risperidone, olanzapine, amisulpiride, quetiapine) and SSRIs are increasingly being used in autism, with encouraging results, but a risk-benefit ratio of pharmacotherapy is essential with due weight being given to the side-effects of medication. Despite symptomatic improvement with medication, one should remain cautious about long-term use of psychotropics. It is also important to recognize that psychotropics can sometimes worsen behaviour, and can produce iatrogenic symptoms. Certain anti-epileptic medication and psychotropic drugs are metabolized by the same cytochrome P450 isoenzymes in the liver. In such circumstances, the addition of a psychotropic agent may drastically alter the levels of the anti-epileptic medication and vice versa. It is suggested that specialist clinics should be involved when one is considering complex medication regimes, experimental drugs, polypharmacy, or if patients show unusual side-effects or is drug resistant.

4.1.62. King, B.H., Wright, D.M., Handen, B.L., Sikich, L., Zimmerman, A.W., McMahon, W., Cantwell, E., Davanzo, P.A., Dourish, C.T., Dykens, F.M., Hooper, S.R., Jaselskis, C.A., Leventhal, B.L., Levitt, J., Lord, C., Lubetsky, M.J., Myers, S.M., Ozonoff, S., Shah, B.G., Snape, M., Shernoff, E.W., Williamson, K., Cook, E.H. Jr. "Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder." *J Am Acad Child Adolesc Psychiatry* 2001 Jun;40(6):658-65. Publication Types: Clinical Trial, Multicenter Study, Randomized Controlled Trial.

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OBJECTIVE: To test the hypothesis that amantadine hydrochloride is a safe and effective treatment for behavioral disturbances—for example, hyperactivity and irritability—in children with autism. **METHOD:** Thirty-nine subjects (intent to treat; 5-19 years old; IQ > 35) had autism diagnosed according to DSM-IV and ICD-10 criteria using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic. The Aberrant Behavior Checklist-Community Version (ABC-CV) and Clinical Global Impressions (CGI) scale were used as outcome variables. After a 1-week, single-blind placebo run-in, patients received a single daily dose of amantadine (2.5 mg/kg per day) or placebo for the next week, and then bid dosing (5.0 mg/kg per day) for the subsequent 3 weeks. **RESULTS:** When assessed on the basis of parent-rated ABC-CV ratings of irritability and hyperactivity, the mean placebo response rate was 37% versus amantadine at 47% (not significant). However, in the amantadine-treated group there were statistically significant improvements in absolute changes in clinician-rated ABC-CVs for hyperactivity (amantadine -6.4 versus placebo -2.1; $p = .046$) and inappropriate speech (-1.9 versus 0.4; $p = .008$). CGI scale ratings were higher in the amantadine group: 53% improved versus 25% ($p = .076$). Amantadine was well tolerated. **CONCLUSIONS:** Parents did not report statistically significant behavioral change with amantadine. However, clinician-rated improvements in behavioral ratings following treatment with amantadine suggest that further studies with this or other drugs acting on the glutamatergic system are warranted. The design of these and similar drug trials in children with autistic disorder must take into account the possibility of a large placebo response.

4.1.63. Roberts, W., Weaver, L., Brian, J., Bryson, S., Emelianova, S., Griffiths, A.M., MacKinnon, B., Yim, C., Wolpin, J., Koren, G. "Repeated doses of porcine secretin in the treatment of autism: a randomized, placebo-controlled trial." *Pediatrics* 2001 May;107(5):E71. Publication Types: Clinical Trial, Randomized Controlled Trial.

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BACKGROUND AND OBJECTIVES: Anecdotal reports on the efficacy of secretin in autism raised great hopes for the

treatment of children with this disorder. Initial single-dose, randomized, controlled trials failed to demonstrate any therapeutic effects of secretin. The present study is the first to test the outcome of repeated doses and to examine whether there is a subgroup of children who are more likely to achieve positive effects. **METHOD:** Sixty-four children with autism (ages 2-7 years; 55 boys and 9 girls) with a range of intelligence quotient and verbal ability were randomly assigned, in a double-blind manner, to secretin or placebo groups. Children received 2 doses of placebo or porcine secretin, 6 weeks apart. Assessments were performed at baseline and 3 weeks after each injection using several outcome measures. **RESULTS:** There were no group differences on formal measures of language, cognition, or autistic symptomatology. Subgroupings based on cognitive level, the presence or absence of diarrhea, or a history of regression failed to show any significant therapeutic effects of secretin. **CONCLUSION:** No evidence is provided for the efficacy of repeated doses of porcine secretin in the treatment of children with autism. The possible relationship between relief of biological symptoms and enhanced skill performance is discussed.

4.1.64. Coniglio, S.J., Lewis, J.D., Lang, C., Burns, T.G., Subhani-Siddique, R., Weintraub, A., Schub, H., Holden, E.W. "A randomized, double-blind, placebo-controlled trial of single-dose intravenous secretin as treatment for children with autism." *J Pediatr* 2001 May;138(5):649-55. Publication Types: Clinical Trial, Randomized Controlled Trial.

Division of Developmental Pediatrics, The Marcus Institute at Emory University, Atlanta, Georgia, USA.

OBJECTIVE: To determine whether a single injection of intravenous secretin results in measurable improvements in socialization and/or communication skills in children with autism. **STUDY DESIGN:** Sixty subjects with autism were randomly selected and assigned to either treatment or placebo group. Subjects in the treatment group received 2.0 clinical units of secretin per kilogram of body weight as a single intravenous dose. Subjects in the placebo group received normal saline solution. Neurodevelopmental and behavioral assessments were performed for all subjects before injection and at 3 and 6 weeks after injection. **RESULTS:** Assessment of language skills and parents' behavioral assessments revealed no significant differences between the treatment and placebo groups. Raters' assessments of severity of autistic symptoms did not differ for the 2 groups at 6 weeks after injection. A marginally statistically significant improvement in autistic behaviors was seen in the treatment group at 3 weeks after injection ($P = .051$). **CONCLUSIONS:** A single dose of intravenous secretin does not appear to have significant effects on either parents' perception of autistic behaviors or language skills at 6 weeks after injection. Transient, marginally significant improvements in autistic behaviors may occur in some children.

4.1.65. Robinson, T.W. "Homeopathic Secretin in autism: a clinical pilot study." *Br Homeopath J* 2001 Apr;90(2):86-91

Barton House, Beaminster, Dorset, UK.

Autism is a condition characterised by impairments of social communication, social interaction and social imagination. The exact aetiology of autism is unknown but some autistic features have been explained by the 'opioid excess theory' in which excess brain peptide levels have a morphine-like activity. Reduction of peptide levels by administration of the duodenal enzyme Secretin has been found to improve social and language skills in autistic patients. Homeopathic Secretin has been said to produce similar effects. A pilot study was undertaken to study these effects by administration of Secretin to a group of autistic patients. Weekly assessment for 12 weeks was performed by the patients' care workers. Statistical analysis of the mean pre-treatment results compared with the mean treatment results suggested a worsening in the autistic symptoms during treatment. Discussion with the care workers revealed changes and some improvements that were not recordable on the scoring system. Further research into Secretin treatment of autism using a more detailed and customized scoring system would be justified. Following this pilot study a randomised controlled trial of Secretin vs placebo would be appropriate.

4.1.66. Posey, D.J., McDougle, C.J. "Pharmacotherapeutic management of autism." *Expert Opin Pharmacother* 2001 Apr;2(4):587-600. Publication Types: Review, Review, Tutorial.

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There are no medications that are specifically marketed for the treatment of autism. There does exist, however, an extensive body of literature describing both open-label and controlled studies of medications in the treatment of both children and adults with autism. Some of the better-studied medications (including haloperidol and risperidone) are often efficacious in treating associated symptoms of autism but can also cause unacceptable adverse effects. Early studies of serotonin re-uptake inhibitors appear promising but may not be indicated for all age groups. Small, controlled studies of methylphenidate and clonidine indicate a possible role for these medications in the treatment of hyperactivity in autism. No medications have been proven to be efficacious in the treatment of the core social or communication impairment seen in autism. Current pharmacological management is best aimed at target symptoms that have been demonstrated to respond to medication in treatment studies.

4.1.67. Findling, R.L. "Paediatric psychopharmacology: closing the gap between science and practice." *Expert Opin Pharmacother* 2001 Apr;2(4):523-5.

Children and adolescents do not always respond to treatment with psychotropic agents in a similar fashion to adults. Differences in safety and therapeutic response may occur across the life cycle. For example, despite the fact that tricyclic antidepressants are traditionally the 'gold standards' of pharmacotherapy for depressed adults, it does not seem that youths with depression benefit from treatment with these agents [1]. Similarly, it appears that earlier age at onset is associated with a reduced propensity to respond to

neuroleptics for patients with schizophrenia [2]. In addition, young patients have been noted to be at higher risk for developing neuroleptic-induced extrapyramidal side effects when compared to adults [3]. Simply put, what is known about the safety and effectiveness of psychotropic compounds in adults cannot necessarily be presumed to be applicable to teenagers or children.

4.1.68. Van der Does, A.J. "The effects of tryptophan depletion on mood and psychiatric symptoms." *J Affect Disord* 2001 May;64(2-3):107-19. Publication Types: Review, Review, Tutorial.

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BACKGROUND: The number of studies using tryptophan depletion (TD) challenge has increased markedly in the past few years. Recently, a number of negative results have been published, implicating that the effect of TD on mood may be less consistent than previously thought. **METHODS:** The literature on the mood effects of TD in psychiatric patients and healthy volunteers was reviewed. **RESULTS:** TD has a mood-lowering effect in subgroups of recovered depressed patients, patients with seasonal affective disorder and vulnerable healthy subjects. The mood effect in former patients is of a different quality, however, than the effect in healthy subjects. Some recent negative studies in depression might be explained by insufficient lowering of plasma tryptophan levels. Preliminary evidence exists for an effect of TD on bulimia nervosa, autism, aggression and substance dependence. **CONCLUSIONS:** The effects of TD on mood may be more consistent than suggested by a number of recent negative studies. Response to TD in recovered depressed patients is associated with prior treatment. However, even in SSRI-treated patients the relapse rates are not higher than 50-60%, which needs to be explained. The clinical usefulness of the response to TD in recovered patients (prediction of relapse after treatment discontinuation) and in symptomatic patients (prediction of treatment refractoriness) deserves more research attention. Further suggestions for future research include the cognitive effects of TD in recovered depressed patients and the effect of dietary habits on response to TD.

4.1.69. Volkmar, F.R. "Pharmacological interventions in autism: theoretical and practical issues." *J Clin Child Psychol* 2001 Mar;30(1):80-7. Publication Types: Review, Review, Tutorial.

Child Study Center, Yale University, P.O. Box 207900, New Haven, CT 06520, USA. fred.volkmar@yale.edu

Focused on issues of drug treatment in relation to autism. Pharmacological treatment studies in autism are complicated by various factors including a tremendous range of syndrome expression, a lack of robust animal models of the disorder, and various methodological problems. Theories have tended to follow treatments, and various neurochemical systems have

been the focus of study. Neurochemical systems potentially implicated include those involving dopamine, norepinephrine, serotonin, and neuropeptides. The dopaminergic system has been the most extensively studied. Treatments developed are effective relative to certain disabling symptoms but "core" problems (e.g., in social relatedness and communication) appear less responsive to medications. The development of new approaches to assessment, including integration of behavioral and pharmacological approaches, is an important research priority.

4.1.70. Rapport, M.D. "Bridging theory and practice: conceptual understanding of treatments for children with attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism, and depression." *J Clin Child Psychol* 2001 Mar;30(1):3-7.

University of Central Florida, Department of Psychology, P.O. Box 161390, Orlando, FL 32816-1390, USA.

Serves as an introduction to a special edition of the journal on bridging theory and clinical practice for childhood disorders. Issues concerning the current trend of developing and evaluating new treatments devoid of a theoretical perspective are discussed. A conceptual model of child psychopathology is presented to illustrate the relevance and interplay between theory and the design and evaluation of treatments with particular emphasis on the selection and measurement of target behaviors. The means by which theory and empirical evidence interact and their relevance to understanding particular childhood disorders are discussed and emphasize the need for theoretical and conceptual models that describe the linkages among hypothesized brain substrates, cognitive function, behavior, and the environment to augment the development of potent biological and psychological interventions.

4.1.71. Kobayashi, R., Takenoshita, Y., Kobayashi, H., Kamijo, A., Funaba, K., Takarabe, M. "Early intervention for infants with autistic spectrum disorders in Japan." *Pediatr Int* 2001 Apr;43(2):202-8.

Department of Social Work, Tokai University School of Health Sciences, Kanagawa, Japan. ryuji@is.icc.u-tokai.ac.jp

BACKGROUND: To date, many researchers in Japan have assumed that the cause of autistic spectrum disorders is attributable to some disorder in the ability of the child. However, we have been working on the premise that autistic spectrum disorders are brought about by relationship disturbances in early infancy and have been attempting to validate this hypothesis through early intervention. **METHODS:** We have examined the developmental process of affective communication in infants with autistic spectrum disorders. We have postulated that approach-avoidance motivational conflict (Richer) is the primary factor impeding the development of affective communication and have focused therapeutic intervention on this perspective. **RESULTS:** As a result, attachment behavior was markedly improved in children, but affective communication with their mothers was

not. Examining the mothers' images of themselves in infancy in mother-infant psychotherapy, problems that the mothers had themselves in infancy with attachment behavior to their own mothers affected the mothers' internal representation of their children, leading to active evolution of mother-child interaction and development of affective communication between the mother and child. **CONCLUSIONS:** In this context, the basis and significance of the internal representation of both parties being determinants in the quality of mother-child communication are discussed. Our goal in early intervention is not the elevation of a child's linguistic-cognitive abilities, but the creation of a comforting relationship in which both parent and child can live securely, without strain.

4.1.72. Furlano, R.I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M.A., Davies, S.E., Berelowitz, M., Forbes, A., Wakefield, A.J., Walker-Smith, J.A., Murch, S.H. "Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism." *J Pediatr* 2001 Mar;138(3):366-72.

University Department of Paediatric Gastroenterology, the Inflammatory Bowel Diseases Study Group, Royal Free and University College School of Medicine, London, United Kingdom.

OBJECTIVES: We have reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism. The aims of this study were to characterize this lesion and determine whether LNH is specific for autism. **METHODS:** Ileo-colonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms. Blinded comparison was made with 8 children with histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease, and 14 with ulcerative colitis. Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness. **RESULTS:** Histology demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of all other groups including patients with inflammatory bowel disease. CD8(+) density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups; and CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial, but not lamina propria, glycosaminoglycans were disrupted. However, the epithelium was HLA-DR(-), suggesting a predominantly T(H)2 response. **INTERPRETATION:** Immunohistochemistry confirms a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected. This is consistent with increasing evidence for gut epithelial dysfunction in autism.

4.1.73. Humble, M., Bejerot, S., Bergqvist, P.B., Bengtsson, F. **"Reactivity of serotonin in whole blood: relationship with drug response in obsessive-compulsive disorder."** *Biol Psychiatry* 2001 Feb 15;49(4):360-8. Publication Types: Clinical Trial, Multicenter Study, Randomized Controlled Trial.

Psychiatry of Northern Dalecarlia, Mora Hospital, Mora, Sweden.

BACKGROUND: Obsessive-compulsive disorder responds almost only to potent serotonin reuptake inhibitors. Previous studies have suggested a relation between serotonergic function and clinical outcome in serotonin reuptake inhibitor treatment of obsessive-compulsive disorder. **METHODS:** In a randomized, double-blind trial, comparing clomipramine, paroxetine, and a placebo in obsessive-compulsive disorder, serotonin levels in whole blood (WB-5-HT) were measured at baseline, after 1 week, and after 4 weeks of treatment and related to clinical outcome in 36 patients. **RESULTS:** In patients treated with serotonin reuptake inhibitors there was a pronounced decrease of WB-5-HT, variable after 1 week and uniformly maximal after 4 weeks. The decrease of WB-5-HT after 1 week of serotonin reuptake inhibitor treatment correlated negatively with clinical outcome after 12 weeks ($r = -.61$, $p = .0006$); hence, patients with slower WB-5-HT reactivity eventually responded better to treatment. Baseline WB-5-HT, but not WB-5-HT reactivity, was related to season. Depression, autistic traits, and previous serotonin reuptake inhibitor treatment predicted nonresponse. **CONCLUSIONS:** A fast decrease of WB-5-HT was associated with poor clinical outcome. This may be related to faster serotonin efflux from platelets, which has previously been linked to autism. Further studies are necessary to identify the underlying mechanism and discern whether serotonin reuptake inhibitor-induced WB-5-HT decrease is clinically useful.

4.1.74. Coupland, N.J. **"Social phobia: etiology, neurobiology, and treatment."** *J Clin Psychiatry* 2001;62 Suppl 1:25-35. Publication Types: Review, Review, Tutorial.

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Social phobia is a common and often disabling condition, with an etiology that is not established. There is evidence at several levels for an interplay of biological and psychological processes in social phobia. Genetic studies show that both genetic and environmental factors are important, with evidence pointing to associations with 2 genetic conditions, autism and fragile X syndrome. Behavioral inhibition has emerged as an important precursor to social phobia and possibly to other anxiety disorders. Epidemiologic and clinical studies have suggested that factors within the family environment, such as overprotection, overcontrol, modeling of anxiety, criticism, and in some cases abuse, can play a role in the development of social phobia. During childhood, complex interactions between brain system disturbances that mediate responses to negative social cues and factors in the social setting may lead to the development of a distorted set of internal "blueprints" for social behavior. The impact of severe social anxiety on brain systems that mediate behavioral

change may prevent patients from learning better "blueprints." These can be taught through cognitive-behavioral therapies. The effective control of social anxiety with medications enables patients to recover; whether recovery can last after discontinuation of medications may depend on whether a new "blueprint" has been developed and whether stable changes in affected brain systems have occurred. Neuroimaging techniques are at the early stage of identifying abnormalities at the neurotransmitter and systems levels.

4.1.75. Luiselli, J.K., Blew, P., Thibadeau, S. **"Therapeutic effects and long-term efficacy of antidepressant medication for persons with developmental disabilities. Behavioral assessment in two cases of treatment-resistant aggression and self-injury."** *Behav Modif* 2001 Jan;25(1):62-78.

May Center for Child Development, Chatham, MA, USA.

Recent advances in pharmacological treatment of severe behavior disorders in persons with developmental disabilities suggest the use of antidepressant medication for therapeutic management. This research evaluated two antidepressant medications for treatment-resistant aggression and self-injury exhibited by two persons with developmental disabilities. Behavioral assessment data documented that sertraline (a serotonin selective reuptake inhibitor) was effective in reducing self-injurious behaviors in a 20-year-old man with severe mental retardation and clomipramine (a tricyclic antidepressant) was associated with the elimination of aggressive behavior in a 14-year-old boy with autism. Clinical effects from the medications were measured in relation to and shown to be a function of dosage level. Extended follow-up assessments revealed maintenance of treatment gains with continued medication administration.

4.1.76. Luiselli, J.K., Blew, P., Keane, J., Thibadeau, S., Holzman, T. **"Pharmacotherapy for severe aggression in a child with autism: "open label" evaluation of multiple medications on response frequency and intensity of behavioral intervention."** *J Behav Ther Exp Psychiatry* 2000 Sep-Dec;31(3-4):219-30. Publication Types: Evaluation Studies.

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Many persons who have developmental disabilities and challenging behaviors are treated with multiple medications combined with nonpharmacological approaches. However, the comparative effects from pharmacotherapy frequently are not assessed empirically, do not include corollary behavioral measures, and are not evaluated in the long term. The present single-case study incorporated behavioral assessment methodology in an "open label" evaluation of anticonvulsant (clonazepam), beta-blocking (propranolol), and antidepressant (sertraline and clomipramine) medications on severe aggression in a child with autism. Clinically significant reductions in aggressive behavior were attained with the administration of clomipramine and the reductive effects from the medication persisted for 1.7 years. In addition, clomipramine was associated with the elimination of crisis

intervention procedures that had been required to manage the child's aggression. These findings add to the clinical literature describing effective treatment of serious behavior disorders in persons with developmental disabilities using antidepressant medication.

4.1.77. Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J.O., Chen, T.J., Comings, D.E. "Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors." *J Psychoactive Drugs* 2000 Nov;32 Suppl:i-iv, 1-112. Publication Types: Review, Review, Academic.

Department of Biological Sciences, University of North Texas, Denton, Texas, USA.

The dopaminergic system, and in particular the dopamine D2 receptor, has been implicated in reward mechanisms. The net effect of neurotransmitter interaction at the mesolimbic brain region induces "reward" when dopamine (DA) is released from the neuron at the nucleus accumbens and interacts with a dopamine D2 receptor. "The reward cascade" involves the release of serotonin, which in turn at the hypothalamus stimulates enkephalin, which in turn inhibits GABA at the substantia nigra, which in turn fine tunes the amount of DA released at the nucleus accumbens or "reward site." It is well known that under normal conditions in the reward site DA works to maintain our normal drives. In fact, DA has become to be known as the "pleasure molecule" and/or the "antistress molecule." When DA is released into the synapse, it stimulates a number of DA receptors (D1-D5) which results in increased feelings of well-being and stress reduction. A consensus of the literature suggests that when there is a dysfunction in the brain reward cascade, which could be caused by certain genetic variants (polygenic), especially in the DA system causing a hypodopaminergic trait, the brain of that person requires a DA fix to feel good. This trait leads to multiple drug-seeking behavior. This is so because alcohol, cocaine, heroin, marijuana, nicotine, and glucose all cause activation and neuronal release of brain DA, which could heal the abnormal cravings. Certainly after ten years of study we could say with confidence that carriers of the DAD2 receptor A1 allele have compromised D2 receptors. Therefore lack of D2 receptors causes individuals to have a high risk for multiple addictive, impulsive and compulsive behavioral propensities, such as severe alcoholism, cocaine, heroin, marijuana and nicotine use, glucose bingeing, pathological gambling, sex addiction, ADHD, Tourette's Syndrome, autism, chronic violence, posttraumatic stress disorder, schizoid/avoidant cluster, conduct disorder and antisocial behavior. In order to explain the breakdown of the reward cascade due to both multiple genes and environmental stimuli (pleiotropism) and resultant aberrant behaviors, Blum united this hypodopaminergic trait under the rubric of a reward deficiency syndrome.

4.1.78. Hayashi, E. "Effect of melatonin on sleep-wake rhythm: the sleep diary of an autistic male." *Psychiatry Clin Neurosci* 2000 Jun;54(3):383-4.

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This study reports on melatonin treatment in autism. A 14-year-old autistic male with severe mental retardation was given melatonin in a dose of 6 mg at 9:00 pm (C1) or 11:00 pm (C2). His parents kept a sleep diary. In C1, he often experienced early morning waking and fragmented night sleep but in C2, night sleep was prolonged and sleep-wake rhythm was improved. Suitable medication time, therefore, improved the sleep-wake rhythm.

4.1.79. Buitelaar, J.K., Willemsen-Swinkels, S.H. "Medication treatment in subjects with autistic spectrum disorders." *Eur Child Adolesc Psychiatry* 2000;9 Suppl 1:185-97. Publication Types: Review, Review, Tutorial.

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Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous. Twin and family genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair strategy has found a promising linkage to a region on chromosome 7. In 10-15 % of the cases autism is due to associated medical conditions that affect normal brain functioning. Post-mortem studies on small case series report cellular abnormalities in the limbic system and cerebellum. Between 10 and 20 % of subjects with autism have macrocephalia, which is in accordance with MRI findings of an increased total brain tissue volume and enlargement most prominent in the occipital and parietal lobes. The most robust and well-replicated neurobiological abnormality in autism is an elevation of whole blood serotonin found in over 30% of the patients. Pharmacological interventions with serotonin reuptake blockers or with atypical neuroleptics that block both dopamine (D2) and serotonin (5-HT2) receptors seem to offer clinical benefit and merit further study.

4.1.80. Chabane, N., Leboyer, M., Mouren-Simeoni, M.C. "Opiate antagonists in children and adolescents." *Eur Child Adolesc Psychiatry* 2000;9 Suppl 1:144-50. Publication Types: Review, Review, Tutorial.

Service de Psychopathologie de l'Enfant et de l'Adolescent, H pital Robert Debre, Paris, France.

Naltrexone a pure opioid antagonist, well tolerated in young patients, has been found to be an interesting treatment in some disorders in children and adolescents. Naltrexone has been first tried in mental retardation and autism disorders in children and adolescents. Symptoms like self-injury behaviours, hyperactivity, stereotyped and ritualistic conducts appear to be improved in a subgroup of children with the opiate antagonist. But new controlled studies still need to be done before recommending naltrexone in autism. Preliminary results in the treatment of alcoholic adolescents seem to support the efficacy of naltrexone on abstinence when combined with a supportive psychotherapy. In adults, results found with the use of naltrexone in eating disorders are different, when considering the duration and the dosage of the treatment and the kind of eating disorder (bulimia, binge

eating or anorexia nervosa). Studies in children and adolescents are needed before proposing naltrexone in eating disorders. We resumed here the results found with this treatment in these indications.

4.1.81. Gillberg, C. "Typical neuroleptics in child and adolescent psychiatry." *Eur Child Adolesc Psychiatry* 2000;9 Suppl 1:12-8. Publication Types: Review, Review, Tutorial.

Queen Silvia Children's University Hospital, Goteborg, Sweden.

This paper reviews the use of typical ("old") neuroleptics in the treatment of child and adolescent psychiatric disorders. Very few methodologically sound papers have been published in the field. It is concluded that typical neuroleptics should be used sparingly and only in severe and incapacitating disorders such as some psychotic conditions and handicapping tic disorders. Side effects have to be very carefully monitored.

4.1.82. Dunn-Geier, J., Ho, H.H., Auersperg, E., Doyle, D., Eaves, L., Matsuba, C., Orrbine, E., Pham, B., Whiting, S. "Effect of secretin on children with autism: a randomized controlled trial." *Dev Med Child Neurol* 2000 Dec;42(12):796-802. Publication Types: Clinical Trial, Randomized Controlled Trial.

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To determine the effect of intravenous porcine secretin on autistic behaviours in children aged 2 to 7 years, the effects of secretin on (1) performance on a standardized language measure, and (2) autistic behaviours, as rated by parents and child development professionals was examined. Employing a randomized, double-blind, placebo-controlled design, 95 participants were assigned to one of two groups and administered a single dose of either secretin or placebo. A follow-up assessment was conducted 3 weeks after the injection. No significant differences in language or autistic behaviour measures were observed at the 3-week follow-up between the groups. Also, there was no significant difference in the proportion of individuals who improved by $> = 6$ points on the language measure at follow-up. This study showed no significant effects of secretin on children with autism. Our results are consistent with a systematic review of randomized controlled trials evaluating the effect of secretin in children with autism.

4.1.83. Klinger, L.G., Renner, P. "Performance-based measures in autism: implications for diagnosis, early detection, and identification of cognitive profiles." *J Clin Child Psychol* 2000 Dec;29(4):479-92. Publication Types: Review, Review, Tutorial.

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Provides a critical review of performance-based assessment measures in autism. Currently, performance-based measures of autism are being explored in two domains: structured play sessions and cognitive-neuropsychological assessments.

Structured play sessions are designed to elicit the behavioral symptoms associated with autism to provide a consistent and valid means of early detection and diagnosis of autism across different evaluators and settings. These structured play sessions provide a supplement to diagnostic instruments based on parental report. Cognitive-neuropsychological tasks have been used to identify possible underlying cognitive impairments in autism including executive function, theory of mind, selective attention, and abstraction. Currently, cognitive tasks are useful in treatment planning but are inappropriate for diagnostic purposes. Important goals for the future will be to integrate parent-report diagnostic interviews and structured play observations and to identify a profile of cognitive impairments that are specific to pervasive developmental disorders that can be incorporated into diagnostic protocols.

4.1.84. Vitiello, B. "Current research highlights in child and adolescent psychopharmacology." *Curr Psychiatry Rep* 2000 Apr;2(2):110-6. Publication Types: Review, Review, Tutorial.

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Recent efforts to stimulate research in pediatric psychopharmacology have resulted in increased interest in the effects of psychotropic medications in children and adolescents. This interest is reflected in the number of studies that have been reported or initiated during the past year. As a means of providing a brief update on the progress of child psychopharmacology, research reports either published or presented at national meetings in 1999 are selectively reviewed here. Relevant initiatives recently started under the sponsorship of the National Institute of Mental Health (NIMH) are also reviewed. Most studies have been directed at testing treatments of attention deficit hyperactivity disorder (ADHD), but also studies of the selective serotonin reuptake inhibitors in patients with obsessive compulsive disorder, depression, and anxiety disorders are well represented. The efforts of NIMH to focus on effectiveness research and direct comparisons of pharmacologic, psychosocial, and combined treatment modalities are apparent in recent initiatives in ADHD and depression. Research of treatments for youths with bipolar disorder, schizophrenia, autism, and eating disorders is still scanty and in urgent need of expansion.

4.1.85. Tuchman, R. "Treatment of seizure disorders and EEG abnormalities in children with autism spectrum disorders." *J Autism Dev Disord* 2000 Oct;30(5):485-9.

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The treatment of seizure disorders EEG epileptiform abnormalities without epilepsy in children with autism spectrum disorders (ASD) is considered within the context of the relationship of epilepsy and epileptiform disorders to language, behavior, and cognition. There is an increased prevalence of both epilepsy and abnormal potentially

epileptogenic activity in children with ASD. Anecdotal evidence suggests that the use of anticonvulsants to treat epileptiform discharges thought to be producing dysfunction in selected aspects of cognition, language, or behavior makes a positive difference in a subgroup of children with ASD, but there is inadequate evidence on which to base specific recommendations. There is, at present, no scientific justification for considering epilepsy surgery in children with ASD in the absence of intractable clinical seizures.

4.1.86. Gupta, S. "Immunological treatments for autism." *J Autism Dev Disord* 2000 Oct;30(5):475-9.

Division of Basic and Clinical Immunology, Medical Sciences I, University of California, Irvine 92697, USA. sgupta@uci.edu

Several investigators, including ourselves, have reported significant changes in various immune responses in children with autism. These changes demonstrate dysregulation of the immune system (deficiency in some components of the immune system and excesses in others). In addition, certain genes in the major histocompatibility complex (that regulates immune responses) appear to be involved in autism. Based upon immunological abnormalities, various treatment modalities have been applied to children with autism. In this brief review, these immunological changes and various biological therapies are analyzed and summarized.

4.1.87. Page, T. "Metabolic approaches to the treatment of autism spectrum disorders." *J Autism Dev Disord* 2000 Oct;30(5):463-9.

Department of Neurosciences, University of California, San Diego, USA.

Although the exact prevalence of metabolic abnormalities in autism spectrum disorders is unknown, several metabolic defects have been associated with autistic symptoms. These include phenylketonuria, histidinemia, adenylosuccinate lyase deficiency, dihydropyrimidine dehydrogenase deficiency, 5'-nucleotidase superactivity, and phosphoribosylpyrophosphate synthetase deficiency. When the metabolic consequences of an enzyme defect are well defined (e.g., phenylketonuria, 5'-nucleotidase superactivity), treatment with diet, drugs, or nutritional supplements may bring about a dramatic reduction in autistic symptoms. This review evaluates evidence for metabolic etiologies in autism spectrum disorders, as well as for the efficacy of dietary and vitamin treatments. The relationship between gastrointestinal abnormalities and autism spectrum disorders is also considered.

4.1.88. Aman, M.G., Langworthy, K.S. "Pharmacotherapy for hyperactivity in children with autism and other pervasive developmental disorders." *J Autism Dev Disord* 2000 Oct;30(5):451-9. Publication Types: Review, Review, Tutorial.

The Nisonger Center for Mental Retardation and Developmental Disabilities, Ohio State University, Columbus, USA.

We reviewed pharmacological treatments used in children with autism and PDD-NOS who present with hyperactive symptoms. Some 41 studies were identified from the following drug categories: antipsychotics (n = 13), serotonin reuptake inhibitors (n = 3), anti-anxiety drugs (n = 4), psychostimulants (n = 10), alpha adrenergic agonists (n = 2), opiate blockers (n = 7), and other drugs (n = 2). Empirical evidence for significant reductions in hyperactive symptoms was strongest for the antipsychotics, psychostimulants, and naltrexone. Most studies have focused on the reduction of overactivity, and more emphasis needs to be placed on distractibility and attentional variables. A theoretical model was proposed in which participants' attentional performance may be used to predict clinical response to psychostimulants. More carefully controlled and comprehensive studies of hyperactivity are badly needed in these children.

4.1.89. King, B.H. "Pharmacological treatment of mood disturbances, aggression, and self-injury in persons with pervasive developmental disorders." *J Autism Dev Disord* 2000 Oct;30(5):439-45. Publication Types: Review, Review, Tutorial.

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Aggression, self-injury, and mood disturbances in persons with autistic disorders, while not uncommon, do not constitute core features of autism. Moreover, these problems can occur for a variety of reasons, which need to be assessed in order to plan appropriate and frequently combined (behavioral-pharmacological) treatments. Drugs acting primarily in the dopaminergic, serotonergic, adrenergic, opioidergic, and glutamatergic systems all have been explored in the treatment of aggression and self-injury. While no single drug or class of medication has yet emerged as consistently effective, a number of drugs appear promising. Advances in the assessment of aggressive behaviors, the identification of predictors of drug response, and additional controlled clinical drug trials specifically aimed at these target behaviors are essential in improving the approach to these problematic behaviors in the context of autistic disorder.

4.1.90. McDougle, C.J., Kresch, L.E., Posey, D.J. "Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors." *J Autism Dev Disord* 2000 Oct;30(5):427-35.

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Repetitive thoughts and behavior are considered integral and core components of autistic disorder. Results from recent studies suggest that the types of repetitive thoughts and behavior of adults with autism and those with obsessive-compulsive disorder (OCD) may be different. Serotonin reuptake inhibitors (SRIs), the primary drug treatment for patients with OCD, may reduce the repetitive phenomena of some autistic patients. Two controlled studies of the nonselective SRI clomipramine have shown the drug to be more efficacious than the relatively selective norepinephrine

reuptake inhibitor desipramine and placebo in children with autism. One controlled study of the selective SRI fluvoxamine found it to be significantly better than placebo for reducing repetitive phenomena and aggression in adults with autistic disorder. Additional research is needed.

4.1.91. Weller, E.B., Weller, R.A., Davis, G.P. "Use of venlafaxine in children and adolescents: a review of current literature." *Depress Anxiety* 2000;12 Suppl 1:85-9. Publication Types: Review, Review, Tutorial.

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Pediatric psychopharmacology is hindered by the relative lack of controlled, empirical clinical trials [Shatzberg and Nemeroff, 1998: Washington, D.C.: The American Psychiatric Press, Inc. p 301-306]. Psychiatric disorders in children and adolescents carry considerable morbidity, impede development, and carry a significant mortality by suicide. Therefore, there is a need for studies of antidepressants and other psychotropics in children and adolescents. This article reviews the preliminary evidence that venlafaxine (Effexor), a novel antidepressant, may be useful in children and adolescents with a variety of psychiatric disorders.

4.1.92. Handen, B.L., Johnson, C.R., Lubetsky, M. "Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder." *J Autism Dev Disord* 2000 Jun;30(3):245-55. Publication Types: Clinical Trial, Randomized Controlled Trial.

University of Pittsburgh School of Medicine, Pennsylvania, USA.

Thirteen children (ages 5.6 to 11.2 years) with autism and symptoms of attention-deficit hyperactivity disorder (ADHD) participated in a double-blind, placebo-controlled crossover study of methylphenidate (0.3 and 0.6 mg/kg per dose). Eight subjects responded positively, based upon a minimum 50% decrease on the Conners Hyperactivity Index. Ratings of stereotypy and inappropriate speech, which are often associated with autistic core features, also decreased. However, no changes were found on the Child Autism Rating Scale, a global assessment of autistic symptomatology. Significant adverse side effects occurred in some children including social withdrawal and irritability, especially at the 0.6 mg/kg dose. Results suggest that methylphenidate can be efficacious for children with autism and ADHD symptoms. However, this group of children seems to be particularly susceptible to adverse side effects.

4.1.93. Van Ree, J.M., Niesink, R.J., Van Wolfswinkel, L., Ramsey, N.F., Kornet, M.M., Van Furth, W.R., Vanderschuren, L.J., Gerrits, M.A., Van den Berg, C.L. "Endogenous opioids and reward." *Eur J Pharmacol* 2000 Sep 29;405(1-3):89-101. Publication Types: Review, Review, Tutorial.

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The discovery of endogenous opioids has markedly influenced the research on the biology of addiction and reward brain processes. Evidence has been presented that these brain substances modulate brain stimulation reward, self-administration of different drugs of abuse, sexual behaviour and social behaviour. There appears to be two different domains in which endogenous opioids, present in separate and distinct brain regions, are involved. One is related to the modulation of incentive motivational processes and the other to the performance of certain behaviours. It is concluded that endogenous opioids may play a role in the vulnerability to certain diseases, such as addiction and autism, but also when the disease is present, such as alcoholism.

4.1.94. Hunsinger, D.M., Nguyen, T., Zebraski, S.E., Raffa, R.B. "Is there a basis for novel pharmacotherapy of autism?" *Life Sci* 2000 Aug 25;67(14):1667-82. Publication Types: Review, Review, Tutorial.

Temple University School of Pharmacy, Philadelphia, PA 19140, USA.

No medication has yet been shown to consistently alter the symptoms or the course of autism in the majority of patients. The present pharmacotherapy is mainly palliative and sometimes effective in attenuating specific behaviors. The search for better treatment involves examination of the underlying pathophysiology, the genetic or environmental etiology (including possible iatrogenic causes), and assessment of the clinically-generated evidence of efficacy, including serendipitous or unexplained findings. Subtle neuroanatomic and neurochemical changes are being explored and there are anecdotal reports or limited clinical trials that suggest some therapy might be possible. Secretin is a surprising recent addition to the list of candidates. The pharmacologic mechanism by which these agents might provide such effect is not clear, but hypotheses are beginning to emerge. In addition, the prevention of some uncertain number of autism cases is being investigated by examination of certain vaccinations as putative causative or contributory factors. These topics are reviewed in this article, which has the additional purpose of stimulating novel drug discovery efforts for this enigmatic disorder.

4.1.95. Murphy, J.V., Wheless, J.W., Schmoll, C.M. "Left vagal nerve stimulation in six patients with hypothalamic hamartomas." *Pediatr Neurol* 2000 Aug;23(2):167-8.

Pediatric Epilepsy Research Center, Children's Mercy Hospital, Kansas City, Missouri 64108, USA.

Six patients with medically refractory epilepsy secondary to hypothalamic hamartomas were treated with intermittent stimulation of the left vagal nerve. Three of the patients had remarkable improvements in seizure control. Four of these six patients had severe autistic behaviors. Striking improvements in these behaviors were observed in all four during treatment with intermittent stimulation. This finding suggests that vagal nerve stimulation can control seizures and autistic behaviors in patients with hypothalamic hamartomas.

4.1.96. Jung, T.P., Makeig, S., Westerfield, M., Townsend, J., Courchesne, E., Sejnowski, T.J. "Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects." *Clin Neurophysiol* 2000 Oct;111(10):1745-58.

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OBJECTIVES: Electrical potentials produced by blinks and eye movements present serious problems for electroencephalographic (EEG) and event-related potential (ERP) data interpretation and analysis, particularly for analysis of data from some clinical populations. Often, all epochs contaminated by large eye artifacts are rejected as unusable, though this may prove unacceptable when blinks and eye movements occur frequently. **METHODS:** Frontal channels are often used as reference signals to regress out eye artifacts, but inevitably portions of relevant EEG signals also appearing in EOG channels are thereby eliminated or mixed into other scalp channels. A generally applicable adaptive method for removing artifacts from EEG records based on blind source separation by independent component analysis (ICA) (Neural Computation 7 (1995) 1129; Neural Computation 10(8) (1998) 2103; Neural Computation 11(2) (1999) 606) overcomes these limitations. **RESULTS:** Results on EEG data collected from 28 normal controls and 22 clinical subjects performing a visual selective attention task show that ICA can be used to effectively detect, separate and remove ocular artifacts from even strongly contaminated EEG recordings. The results compare favorably to those obtained using rejection or regression methods. **CONCLUSIONS:** The ICA method can preserve ERP contributions from all of the recorded trials and all the recorded data channels, even when none of the single trials are artifact-free.

4.1.97. Jansen, L.M., Gispen-de Wied, C.C., Van der Gaag, R.J., ten Hove, F., Willemsen-Swinkels, S.W., Harteveld, E., Van Engeland, H. "Unresponsiveness to psychosocial stress in a subgroup of autistic-like children, multiple complex developmental disorder." *Psychoneuroendocrinology* 2000 Nov;25(8):753-64.

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In this study, we tried to replicate the finding of a diminished cortisol response to stress in autistic-like patients in a more homogenous Multiple Complex Developmental Disorder (MCDD) group. MCDD forms a distinct group within the autistic-like disorders, characterized by impaired regulation of anxiety and affective state, impaired social behavior/sensitivity, and thought disorder. A number of MCDD children develop schizophrenia in adult life. Responses to a psychosocial stressor, consisting of speaking in public while recorded on video, were measured in 10 MCDD children and 12 healthy control children. The public speaking test was imbedded in a two-hour test session, and compared to a control test session. Hypothalamic-pituitary-adrenal (HPA)

responses were measured on salivary cortisol at about 20-minute intervals. Heart rate was measured continuously. Delta AUC's were computed for both heart rate (dAUCHR) and salivary cortisol (dAUCCORT), as a measure of response to the test. The public speaking task resulted in significant responses in heart rate and salivary cortisol in healthy control children, but not in MCDD children. dAUCHR was 3.28+/-2.37 in healthy control children, but -0.09+/-1.73 in MCDD children ($t=3.31$, $P<0.01$). dAUCCORT was 3.22+/-3.16 in healthy control children, but 0.17+/-1.74 in MCDD children ($t=2.72$, $P<0.05$). The impaired responses to psychosocial stress found in MCDD children may be the result of their limited abilities to react adequately to their (social) environment. The same impairment in stress processing has been found in schizophrenia, and might be a factor in the vulnerability of these MCDD children to develop schizophrenia.

4.1.98. Tsuchiya, H., Hayashi, T. "A possible link between beta-carboline metabolism and infantile autism." *Med Hypotheses* 2000 Sep;55(3):215-7.

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Benzodiazepine receptors and abnormal hepatic metabolism have been suggested to participate in several neuropsychiatric disorders including autism. Neuropsychosocially active beta-carboline alkaloids as the potent ligands for benzodiazepine receptors are endogenously produced and exogenously supplied much more than benzodiazepines. 1-Methyl-1,2,3,4-tetrahydro-beta-carboline, a predominant alkaloid in humans and foodstuffs, is metabolically hydroxylated in liver. Although its *in vivo* levels show no difference between autistic and healthy children, the metabolic 6-hydroxylation is significantly decreased in autistic subjects. Therefore, it could be hypothesized that the reduced hepatic metabolism of 1-methyl-1,2,3,4-tetrahydro-beta-carboline to 6-hydroxyl metabolite may be linked to the pathogenesis of infantile autism as suggested for autistic occurrence to involve the pathology similar to hepatic encephalopathy.

4.1.99. Naqvi, S., Cole, T., Graham, J.M. Jr. "Cole-Hughes macrocephaly syndrome and associated autistic manifestations." *Am J Med Genet* 2000 Sep 11;94(2):149-52.

Department of Psychiatry, Cedars-Sinai Medical Center, Thelians Community Mental Health Center, Los Angeles, California, USA.

Based on cases that had been excluded from a previous clinical study of Sotos syndrome, Cole and Hughes [1991: *Am J Med Genet* 41:115-124] reported a new syndrome associated with marked obesity, occasional delayed bone age, distinctive facial anomalies, mental retardation, and progressive postnatal macrocephaly in the context of autosomal dominant familial macrocephaly. Subsequently, Stevenson et al. [1997: *Lancet* 349:1744-1745] emphasized the association of progressive postnatal macrocephaly with autism, and they suggested that this might comprise a recognizable autism syndrome. We report two additional patients with Cole-Hughes syndrome and associated autistic characteristics with attention deficit

hyperactivity disorder. These patients seem to manifest a distinctive behavioral phenotype associated with Cole-Hughes syndrome and they manifest a distinct subgroup of persons with autism that may ultimately shed light on the pathogenesis of this disorder. Copyright 2000 Wiley-Liss, Inc.

4.1.100. Buitelaar, J.K., Willemsen-Swinkels, S.H. "Autism: current theories regarding its pathogenesis and implications for rational pharmacotherapy." *Paediatr Drugs* 2000 Jan-Feb;2(1):67-81. Publication Types: Review, Review, Academic.

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Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous. Twin and family-genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair strategy has found a promising linkage to a region on chromosome 7. In 10 to 15% of cases autism is due to associated medical conditions that affect normal brain functioning. Postmortem studies on small case series report cellular abnormalities in the limbic system and cerebellum. Between 10 and 20% of individuals with autism have macrocephalia, which is in accordance with magnetic resonance imaging (MRI) findings of an increased total brain tissue volume and enlargement most prominent in the occipital and parietal lobes. The most robust and well replicated neurobiological abnormality in autism is an elevation of whole blood serotonin (5-hydroxytryptamine; 5-HT) found in over 30% of patients. Pharmacological interventions with serotonin reuptake inhibitors or with atypical neuroleptics that block both dopamine (D2) and serotonin (5-HT₂) receptors seem to offer clinical benefit and merit further study.

4.1.101. Smith, T., Groen, A.D., Wynn, J.W. "Randomized trial of intensive early intervention for children with pervasive developmental disorder." *Am J Ment Retard* 2000 Jul;105(4):269-85. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Young children with pervasive developmental disorder were randomly assigned to intensive treatment or parent training. The intensive treatment group (7 with autism, 8 with pervasive developmental disorder not otherwise specified—NOS) averaged 24.52 hours per week of individual treatment for one year, gradually reducing hours over the next 1 to 2 years. The parent training group (7 with autism, 6 with pervasive developmental disorder NOS) received 3 to 9 months of parent training. The groups appeared similar at intake on all measures; however, at follow-up the intensive treatment group outperformed the parent training group on measures of intelligence, visual-spatial skills, language, and academics, though not adaptive functioning or behavior problems. Children with pervasive developmental disorder NOS may have gained more than those with autism.

4.1.102. Zuddas, A., Di, Martino, A., Muglia, P., Cianchetti, C. "Long-term risperidone for pervasive developmental disorder: efficacy, tolerability, and discontinuation." *J Child Adolesc Psychopharmacol* 2000. Publication Types: Clinical Trial.

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To investigate the safety (e.g., weight gain, liver function, extrapyramidal side effects, and seizures) and efficacy of the long-term use of risperidone in children and adolescents and to ascertain the effects of drug withdrawal in a semi-naturalistic prospective, subjects with autism or pervasive developmental disorders not otherwise specified (PDDNOS) were treated with risperidone for 6 months after which parents were given the option of continuing for a further 6 months (final assessment at 12 months). Behavioral rating included Childhood Autism Rating Scale (CARS), Child Psychiatric Rating Scale (CPRS), Clinical Global Impression (CGI), and Child-Global Assessment Scale (C-GAS). Risperidone significantly ameliorated behavioral symptoms of PDD in 10 out of 11 subjects, with the effects on core symptoms being of smaller amplitude and of slower onset. No loss of effectiveness was observed in patients who continued risperidone for 12 months, while a relapse of associated behavioral symptoms occurred in the others. Weight gain was common, although the rate of increase lessened over a period of time; after drug withdrawal, considerable weight loss was observed in the patient who had previously shown the most significant increase. After 6 months of therapy, two patients developed facial dystonia: this disappeared after reducing dosage in one case, after drug discontinuation in the other. Amenorrhea was also observed, but no changes in liver function, blood tests or EEG were reported. The data indicate that risperidone is an effective and relatively safe drug for long term treatment of behavioral disruption in autistic children and adolescents.

4.1.103. Sandler, R.H., Finegold, S.M., Bolte, E.R., Buchanan, C.P., Maxwell, A.P., Vaisanen, M.L., Nelson, M.N., Wexler, H.M. "Short-term benefit from oral vancomycin treatment of regressive-onset autism." *J Child Neurol* 2000 Jul;15(7):429-35.

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In most cases symptoms of autism begin in early infancy. However, a subset of children appears to develop normally until a clear deterioration is observed. Many parents of children with "regressive"-onset autism have noted antecedent antibiotic exposure followed by chronic diarrhea. We speculated that, in a subgroup of children, disruption of indigenous gut flora might promote colonization by one or more neurotoxin-producing bacteria, contributing, at least in part, to their autistic symptomatology. To help test this hypothesis, 11 children with regressive-onset autism were recruited for an intervention trial using a minimally absorbed oral antibiotic. Entry criteria included antecedent broad-spectrum antimicrobial exposure followed by chronic persistent diarrhea, deterioration of previously acquired skills,

and then autistic features. Short-term improvement was noted using multiple pre- and post-therapy evaluations. These included coded, paired videotapes scored by a clinical psychologist blinded to treatment status; these noted improvement in 8 of 10 children studied. Unfortunately, these gains had largely waned at follow-up. Although the protocol used is not suggested as useful therapy, these results indicate that a possible gut flora-brain connection warrants further investigation, as it might lead to greater pathophysiologic insight and meaningful prevention or treatment in a subset of children with autism.

4.1.104. Posey, D.J., McDougle, C.J. **"The pharmacotherapy of target symptoms associated with autistic disorder and other pervasive developmental disorders."** *Harv Rev Psychiatry* 2000 Jul-Aug;8(2):45-63. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Indiana University School of Medicine, Indianapolis, USA.

Research into the pharmacotherapy of autistic disorder has steadily increased over the past two decades. Several psychoactive medications have shown efficacy for selected symptoms of autistic disorder and can be used to augment critical educational and behavioral interventions that are the mainstays of treatment. A comprehensive review of medication trials conducted in individuals with autistic disorder and other pervasive developmental disorders is presented. The typical antipsychotic haloperidol is the best-studied medication in autistic disorder but is associated with a high rate of dyskinesias. Investigations to date suggest that the atypical antipsychotics such as risperidone have efficacy for certain symptoms of autistic disorder and may be better tolerated than typical antipsychotics. Preliminary results from trials with serotonin-reuptake inhibitors are favorable, although efficacy has not been demonstrated in younger age groups. Recent controlled studies of naltrexone suggest that the drug has minimal efficacy. In two small controlled investigations, clonidine was more effective than placebo for a variety of symptoms, including hyperactivity and irritability; in one of these studies, however, the majority of patients relapsed within several months. Psychostimulants reduced hyperactivity and irritability in one small double-blind crossover study in children with autistic disorder, although these agents are frequently reported to exacerbate irritability, insomnia, and aggression in clinical populations. Recent controlled trials of secretin have not shown efficacy compared to placebo. Several other medications, including buspirone, mood stabilizers, and beta-blockers, have produced symptom reduction in some open-label studies and may warrant controlled investigation.

4.1.105. Shenoy, S., Arnold, S., Chatila, T. **"Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome."** *J Pediatr* 2000 May;136(5):682-7.

Divisions of Hematology-Oncology, Neurology, and Immunology-Rheumatology, Department of Pediatrics,

Washington University School of Medicine and St Louis Children's Hospital, St Louis, MO 63110, USA.

We report a child who developed autoimmune lymphoproliferative syndrome (ALPS) secondary to a heterozygous dominant negative mutation in the death domain of the Fas receptor. Previously developmentally normal, he had symptoms of autism with rapid regression in developmental milestones coincident with the onset of lymphoproliferation and autoimmune hemolytic anemia. Low-dose steroid therapy induced early and complete remission in the ALPS phenotype. There was subjective improvement, followed by objective improvement in speech and developmental milestones. We propose that autism may be part of the autoimmune disease spectrum of ALPS in this child, and this case represents a novel manifestation and target organ involvement in this disease.

4.1.106. Riva, D., Giorgi, C. **"The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours."** *Brain* 2000 May;123 (Pt 5):1051-61.

Developmental Neurology Division, Carlo Besta National Neurological Institute, Milan, Italy. driva@istituto-besta.it

We present data on the intellectual, language and executive functions of 26 children who had undergone surgery for the removal of cerebellar hemisphere or vermal tumours. The children with right cerebellar tumours presented with disturbances of auditory sequential memory and language processing, whereas those with left cerebellar tumours showed deficits on tests of spatial and visual sequential memory. The vermal lesions led to two profiles: (i) post-surgical mutism, which evolved into speech disorders or language disturbances similar to agrammatism; and (ii) behavioural disturbances ranging from irritability to behaviours reminiscent of autism. These data are consistent with the recently acknowledged role of the cerebellum as a modulator of mental and social functions, and suggest that this role is operative early in childhood.

4.1.107. Blatt, S.D., Meguid, V., Church, C.C. **"Sudden infant death syndrome and secretin treatment for autism."** *Curr Opin Pediatr* 2000 Apr;12(2):179-83. Publication Types: Review, Review, Tutorial.

Upstate Medical University, State University of New York, Syracuse 13202, USA.

The Back to Sleep Campaigns remain the greatest influence on the reduction of sudden infant death syndrome. Blatt and Meguid review updates on the effectiveness of these campaigns in reducing sudden infant death syndrome. They also review studies on why parents do not follow this proven advice. The contribution of the risks of other environmental factors are also reviewed. Also discussed are commentaries from a study reviewed last on the link between a prolonged QT electrocardiogram interval and sudden infant death syndrome. Church provides a cogent and timely review of the reported effectiveness of hormone secretin effectiveness in treating children with autism. This newly proposed

treatment has been in the spotlight of the lay public, the popular media, and the scientific community. In short order, secretin as a treatment for autism has moved from a chance observation to the subject of a double-blind, placebo-controlled study.

4.1.108. Erba, H.W. "Early intervention programs for children with autism: conceptual frameworks for implementation." *Am J Orthopsychiatry* 2000 Jan;70(1):82-94.

University of North Carolina at Chapel Hill, USA.

Four diverse early intervention programs for children with autism—discrete trial training, LEAP, floor time, and TEACCH—are described. For each program, the concepts of learning, development, and autism are summarized, intervention procedures are outlined, and connections between theory and practice are illustrated. Research outcomes for each of the four programs are discussed.

4.1.109. Hollander, E., Kaplan, A., Cartwright, C., Reichman, D. "Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report." *J Child Neurol* 2000 Feb;15(2):132-5.

Department of Psychiatry and the Seaver Autism Research Center, Mount Sinai School of Medicine, New York, New York 10029, USA. e_hollander@smtplink.mssm.edu

Autism is characterized by social deficits, communication and language impairments, narrow restricted interests, repetitive behaviors, inattention, and hyperactivity. While selective serotonin reuptake inhibitors have demonstrated efficacy in treating core symptoms of autism, norepinephrine reuptake inhibitors have demonstrated efficacy in symptoms of attention-deficit hyperactivity disorder (ADHD). An open, retrospective clinical study with venlafaxine evaluated its effect on core symptoms of autism as well as associated features of ADHD. Ten consecutive subjects meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), criteria for an autism spectrum disorder were treated with venlafaxine, initiated at 12.5 mg per day and adjusted on a flexible basis. Six of 10 completers were judged to be sustained treatment responders, by scoring 1 (very much improved) or 2 (much improved) on the Clinical Global Impressions improvement scale. Venlafaxine was effective in low dosages (mean, 24.37 mg/day; range, 6.25 to 50 mg/day) and was well tolerated. Improvement was noted in repetitive behaviors and restricted interests, social deficits, communication and language function, inattention, and hyperactivity. Controlled treatment trials with venlafaxine are warranted in autism spectrum disorders.

4.1.110. McDougle, C.J., Scahill, L., McCracken, J.T., Aman, M.G., Tierney, E., Arnold, L.E., Freeman, B.J., Martin, A., McGough, J.J., Cronin, P., Posey, D.J., Riddle, M.A., Ritz, L., Swiezy, N.B., Vitiello, B., Volkmar, F.R., Votolato, N.A., Walson, P. "Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Background and rationale for an initial controlled study of risperidone." *Child Adolesc Psychiatr Clin N Am* 2000 Jan;9(1):201-24. Publication Types: Review, Review, Tutorial.

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This article has reviewed the background and rationale for the choice of risperidone as the first drug to be studied by the RUPP Autism Network. Risperidone has potent effects on 5-HT and DA neuronal systems, both of which have been implicated in the pathophysiology of autism. Unlike the typical antipsychotics, haloperidol and pimozide, which have been shown to be effective for reducing many of the maladaptive behaviors associated with autism, risperidone's 5-HT_{2A}/DA D₂ ratio of receptor blockade appears to produce a lower risk of acute and chronic extrapyramidal side effects, as well as enhanced efficacy for the "negative" symptoms of autism. Indirect clinical and preclinical evidence supports the use of risperidone to treat impaired social behavior, interfering repetitive phenomena, and aggression, targets of pharmacotherapy for many patients with autism. Numerous published open-label trials in children and adolescents with autism and related PDDs and one double-blind, placebo-controlled study in adults suggest that risperidone has promise for the treatment of children and adolescents with autism. Because most of these studies have been short-term, open-label trials in small samples, however, a large-scale controlled study of risperidone in children and adolescents with autism is needed to confirm these results. Finally, because it is likely that children who demonstrate short-term benefit from risperidone will remain on the medication indefinitely, the longer-term effectiveness and safety of risperidone in this population also needs to be determined. The design of this study and the assessments used are described separately.

4.1.111. Flatter, N.L., Blakely, R.D. "Modified structure of the human serotonin transporter promoter." *Mol Psychiatry* 2000 Jan;5(1):110-5.

Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232-6420, USA.

Recently, several studies have reported an association between anxiety traits, affective disorders and autism and alleles of a functional promoter polymorphism (5HTT-LPR) in the human serotonin transporter (5HTT, SERT).¹⁻³ The mechanistic basis for allelic differences in transporter transcription are presently unknown. To explore this issue, we cloned the human 5HTT promoter region from a PAC genomic library and now describe an unreported 381-bp insert between the polymorphic region and the transcription start site. We verified the presence of this novel sequence by Southern hybridization of genomic digests and PCR amplifications from multiple unrelated individuals. Sequence analysis of the novel region reveals a number of canonical transcription factor binding sites (eg AP1, Elk1, NFkappaB) that may be important in controlling the response of the 5HTT gene to regulatory factors. PCR studies of genomic templates reveal a low level of amplification of a deleted template matching the size of the originally reported 5HTT promoter. This deleted template is absent from PAC amplifications, suggesting that the human 5HTT promoter may exhibit in vivo instability. *Molecular Psychiatry* (2000) 5, 110-115.

4.1.112. Liakos, A.M., Bradley, N.K., Magram, G., Muszynski, C. "Hydrocephalus and the reproductive health of women: the medical implications of maternal shunt dependency in 70 women and 138 pregnancies." *Neurol Res* 2000 Jan;22(1):69-88.

Hydrocephalus Research Foundation, Atlanta, GA 30043, USA.

An increasing number of women with cerebrospinal fluid shunts are surviving to child-bearing age, and are making independent decisions in regard to planning their families. As a result, a broad range of interdisciplinary health care professionals will require information about the management of these patients, especially during pregnancy and delivery. The purpose of this ongoing study is to gather comprehensive data from shunted women regarding their clinical history during pregnancy and within the six-month post-partum period. As part of this study, the following questions were addressed: 1. How does maternal shunt dependency influence the course of pregnancy and pregnancy outcomes? 2. What neurosurgical complications characterize this population of patients? 3. What complications of shunt dependency influence obstetrical management including pre-natal testing and delivery? 4. What are the implications of shunt dependency with respect to general reproductive health concerns within this population? A total of 70 respondents, 18-41 years old and accounting for 138 pregnancies, completed a questionnaire providing information on maternal background, medical history, shunt performance during pregnancy, management of delivery, pregnancy outcomes, and unusual complications. One hundred three (103) pregnancies resulted in 105 live births including two surviving sets of twins; of these, 84 occurred in women with ventriculoperitoneal shunts (including both mothers who gave birth to live twins). Four women underwent therapeutic abortions, five delivered pre-term, one mother delivered a stillborn infant, and 16 experienced 32 miscarriages (including two ectopic pregnancies, and 33 fetal losses). Three women had seizures during pregnancy. Nine mothers reported an increase in headache activity during pregnancy. Twelve described abdominal pains during the course of pregnancy with anecdotal reports of increased frequency of painful episodes during the first and third trimesters. Twelve babies were diagnosed with congenital defects, including one pair of fraternal twins individually diagnosed with symmetric parietal foramina. Seven additional children were diagnosed with developmental disabilities including attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), pervasive developmental delay (PDD), and autism. Shunt malfunctions and revisions occurred seven times (four women) during pregnancy, and in 24 pregnancies (13 women) within six months of delivery. One malfunction and revision followed the miscarriage of twins at 12 gestational weeks. No acute malfunctions requiring immediate revision occurred during delivery, although two women reported severe headaches during labor. Transient signs of raised intracranial pressure occurred in 15 mothers over the course of 19 pregnancies which did not require surgical revision of the shunt following delivery or termination of pregnancy. No signs

of shunt malfunction were identified in 100 of the pregnancies described in this series; 31 of these resulting in miscarriage and 69 resulting in live births. This study extends observations made previously to a larger population of shunt dependent mothers, and nearly doubles the amount of data available in our last publication. The results suggest that maternal shunt dependency carries a relatively high incidence of complications for some patients, but that proper management of these patients can lead to normal pregnancy and delivery.

4.1.113. Klein, U., Nowak, A.J. "Characteristics of patients with autistic disorder (AD) presenting for dental treatment: a survey and chart review." *Spec Care Dentist* 1999 Sep-Oct;19(5):200-7.

Munroe-Meyer Institute for Geriatrics and Rehabilitation, Nebraska Medical Center, Omaha 68195-5450, USA.

A group of 43 patients with AD (mean age, 13.5; SD, 5.9 yrs) was identified from the University Hospital School Pediatric Dentistry Clinic. We reviewed the patients' charts to obtain demographic data, dental findings, and the management techniques used for treatment. The patients were divided into groups according to Frankl's categories of behavior, ranging from definitely negative to positive. Descriptive data are provided for each group. Commonly used communications and pharmacological management techniques, as well as physical restraints, enabled us to treat all the patients in the traditional dental setting, when simple procedures were planned. Treatment under general anesthesia in the operating room was necessary in 37% of all patients when comprehensive care was required or difficult procedures were carried out. A questionnaire was also sent out to the caregivers to gather data on patients' nutrition and eating/chewing habits. In the sample surveyed, two-thirds of the individuals reportedly exhibited a normal eating pattern, while 14% pouched food. Soft, sweet, or sticky foods were preferred by 41% of the patients.

4.1.114. McMillin, D.L., Richards, D.G., Mein, E.A., Nelson, C.D. "The abdominal brain and enteric nervous system." *J Altern Complement Med* 1999 Dec;5(6):575-86. Publication Types: Review, Review, Tutorial.

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Conventional medical treatment for neurologic disorders such as epilepsy, migraine, and autism focuses on the brain. Although standard medical treatment is often helpful, the underlying causes of these disorders are not well understood. Furthermore, some individuals respond poorly or not at all to regular medicine. Evidence is accumulating in the medical literature that the enteric nervous system (ENS)-that part of the nervous system associated with the alimentary canal-also plays a role in these disorders. Historically, the concept of an autonomous abdominal nervous system was advocated by Byron Robinson, Johannes Langley, and Edgar Cayce. The work of these three prominent historical figures is considered along with modern view-points on the abdominal nervous system. Complementary therapies that address the nervous system

of the abdomen have potential as useful adjuncts to conventional treatment for certain neurologic disorders.

4.1.115. Posey, D.J., Walsh, K.H., Wilson, G.A., McDougle, C.J. "Risperidone in the treatment of two very young children with autism." *J Child Adolesc Psychopharmacol* 1999;9(4):273-6.

Department of Psychiatry, Indiana University School of Medicine, Indianapolis, USA.

This report describes the use of risperidone in the treatment of two very young children with autistic disorder, a 29-month-old boy and a 23-month-old boy, respectively. These children presented with severe and persistent symptoms of aggression and irritability that had not responded to previous treatment. In both cases, risperidone significantly reduced aggression and improved social relatedness. One patient's treatment with risperidone was complicated by persistent tachycardia and QTc interval prolongation that was dose-related. Consideration should be given to the appropriate use of medication in the treatment of very young children with autism when other interventions do not prove helpful.

4.1.116. Volkmar, F., Cook, E.H. Jr., Pomeroy, J., Realmuto, G., Tanguay, P. "Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues." *J Am Acad Child Adolesc Psychiatry* 1999 Dec;38(12 Suppl):32S-54S. Publication Types: Guideline, Practice Guideline, Review, Review, Tutorial.

AACAP, Communications Department, Washington, DC 20016, USA.

Autism and the related pervasive developmental disorders are characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills, which arise in the first years of life. Although frequently associated with mental retardation, these conditions are distinctive in terms of their course and treatment. These conditions have a wide range of syndrome expression, and their management presents particular challenges for clinicians. Individuals with these conditions can present for clinical care at any point in development. The multiple developmental and behavioral problems associated with these conditions often require the care of multiple providers; coordination of services and advocacy for individuals and their families is important. Early, sustained intervention is indicated, as is the use of various treatment modalities (e.g., pharmacotherapy, special education, speech/communication therapy, and behavior modification).

4.1.117. Zaw, F.K., Bates, G.D., Murali, V., Bentham, P. "Catatonia, autism, and ECT." *Dev Med Child Neurol* 1999 Dec;41(12):843-5.

Department of Psychiatry, Birmingham Children's Hospital, UK. FrankZaw@bhamchildrens.wmids.nhs.uk

We describe the clinical presentation, course, and treatment response of a 14-year-old boy with catatonic stupor. This patient, with a preexisting diagnosis of autism, displayed mutism, akinesia, and an extreme level of rigidity, waxy flexibility, posturing, including the psychological pillow, facial grimacing, and other involuntary movements of his upper extremities. In addition he had symptoms suggestive of a depressive disorder as well as some non-specific psychotic symptoms. Intravenous injection of sodium amytal failed to resolve any motor symptoms, although he showed a good response to the zolpidem test. A course of electroconvulsive therapy (ECT) caused dramatic and sustained relief of catatonic stupor without a change in the symptoms of autism. The presentation of catatonia in autism and the use of ECT in children are discussed, and the available literature reviewed. This is the first description of the use of ECT in the treatment of catatonia coinciding with autism and we confirm its efficacy.

4.1.118. Sandler, A.D., Sutton, K.A., DeWeese, J., Girardi, M.A., Sheppard, V., Bodfish, J.W. "Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder." *N Engl J Med* 1999 Dec 9;341(24):1801-6. Publication Types: Clinical Trial, Randomized Controlled Trial.

Olson Huff Center for Child Development, Thoms Rehabilitation Hospital, Asheville, NC 28803, USA. adsandler@pol.net

BACKGROUND: Secretin is a peptide hormone that stimulates pancreatic secretion. After recent publicity about a child with autism whose condition markedly improved after a single dose of secretin, thousands of children with autistic disorders may have received secretin injections. **METHODS:** We conducted a double-blind, placebo-controlled trial of a single intravenous dose of synthetic human secretin in 60 children (age, 3 to 14 years) with autism or pervasive developmental disorder. The children were randomly assigned to treatment with an intravenous infusion of synthetic human secretin (0.4 microg per kilogram of body weight) or saline placebo. We used standardized behavioral measures of the primary and secondary features of autism, including the Autism Behavior Checklist, to assess the degree of impairment at base line and over the course of a four-week period after treatment. **RESULTS:** Of the 60 children, 4 could not be evaluated - 2 received secretin outside the study, and 2 did not return for follow-up. Thus, 56 children (28 in each group) completed the study. As compared with placebo, secretin treatment was not associated with significant improvements in any of the outcome measures. Among the children in the secretin group, the mean total score on the Autism Behavior Checklist at base line was 59.0 (range of possible values, 0 to 158, with a larger value corresponding to greater impairment), and among those in the placebo group it was 63.2. The mean decreases in scores over the four-week period were 8.9 in the secretin group and 17.8 in the placebo group (mean difference, -8.9; 95 percent confidence interval, -19.4 to 1.6; P=0.11). None of the children had treatment-limiting adverse effects. After they were told the results, 69 percent of the parents of the children in this study said they

remained interested in secretin as a treatment for their children. **CONCLUSIONS:** A single dose of synthetic human secretin is not an effective treatment for autism or pervasive developmental disorder.

4.1.119. Tsai, L.Y. "Psychopharmacology in autism." *Psychosom Med* 1999 Sep -Oct;61(5):651-65. Publication Types: Review, Review, Tutorial.

Child and Adolescent Psychiatric Hospital, University of Michigan Medical School, Ann Arbor 48109-0390, USA.

Autism is a neurobiological disorder. The core clinical features of autism include impairment in social interaction, impairments in verbal and nonverbal communication, and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Autism often has coexisting neuropsychiatric disorders, including seizure disorders, attention deficit hyperactivity disorder, affective disorders, anxiety disorder, obsessive-compulsive disorder, and Tourette disorder. No etiology-based treatment modality has been developed to cure individuals with autism. However, comprehensive intervention, including parental counseling, behavior modification, special education in a highly structured environment, sensory integration training, speech therapy, social skill training, and medication, has demonstrated significant treatment effects in many individuals with autism. Findings from preliminary studies of major neurotransmitters and other neurochemical agents strongly suggest that neurochemical factors play a major role in autism. The findings also provide the rationale for psychopharmacotherapy in individuals with autism. This article reviews studies of neurochemical systems and related psychopharmacological research in autism and related neuropsychiatric disorders. Clinical indications for pharmacotherapy are described, and uses of various medications are suggested. This article also discusses new avenues of investigation that may lead to the development of more effective medication treatments in persons with autism.

4.1.120. Martin, A., Koenig, K., Scahill, L., Bregman, J. "Open-label quetiapine in the treatment of children and adolescents with autistic disorder." *J Child Adolesc Psychopharmacol* 1999;9(2):99-107.

Child Study Center, Yale University School of Medicine, New Haven, Connecticut, USA.

OBJECTIVE: The purpose of this trial was to investigate the short-term safety and efficacy of quetiapine fumarate in the treatment of children and adolescents with autistic disorder (AD). **METHOD:** This was a 16-week, open-label trial that included 6 male subjects with a mean age of 10.9 +/- 3.3 years. All subjects met the DSM-IV criteria for AD and functioned in the mentally retarded range (mild, n = 2; moderate, n = 3; severe, n = 1). Behavioral ratings were obtained at baseline and every four weeks thereafter. **RESULTS:** Overall, there was no statistically significant improvement between baseline and endpoint for the group as a whole. Only two subjects completed 16 weeks of treatment and were considered "responders" by the global improvement item of the Clinical

Global Impression Scale (CGIS). Dosages ranged from 100 to 350 mg/day (1.6-5.2 mg/kg/day). Subjects dropped out prematurely because of lack of response and sedation, limiting further dose increases (n = 3), and because of a possible seizure during the fourth week of treatment (n = 1). Other significant side effects included behavioral activation, increased appetite and weight gain (range, 0.9 to 8.2 kg). **CONCLUSIONS:** Quetiapine was poorly tolerated and associated with serious side effects in this clinical population.

4.1.121. Rossi, P.G., Posar, A., Parmeggiani, A., Pipitone, E., D'Agata, M. "Niaprazine in the treatment of autistic disorder." *J Child Neurol* 1999 Aug;14(8):547-50.

Department of Child Neurology and Psychiatry, Neurological Institute, University of Bologna, Italy. giovanar@alma.unibo.it

Niaprazine is a histamine H1-receptor antagonist with marked sedative properties. It has been employed in subjects with behavior and sleep disorders. No data concerning the use of niaprazine in subjects with autistic disorder are reported in the literature. The authors performed an open study to assess niaprazine efficacy in a sample of 25 subjects with autistic disorder and associated behavior and sleep disorders. Niaprazine was administered at 1 mg/kg/day for 60 days. A positive effect was found in 52% of patients, particularly on hyperkinesia, unstable attention, resistance to change and frustration, mild anxiety signs, heteroaggressiveness, and sleep disorders. Statistical comparison between responders and nonresponders showed no influence on niaprazine effect by age over or under 12 years, presence of neurologic signs, epilepsy, or abnormalities seen on brain imaging. Niaprazine was more efficacious in subjects with a mild or moderate degree of mental retardation. No side effects were observed. Because of its sedative effects and good tolerability, niaprazine can be used as a first-choice drug to improve behavior and sleep disorders in patients with autistic disorder.

4.1.122. Nass, R., Gross, A., Wisoff, J., Devinsky, O. "Outcome of multiple subpial transections for autistic epileptiform regression." *Pediatr Neurol* 1999 Jul;21(1):464-70.

Department of Neurology, New York University Medical Center, New York 10016, USA.

Treatment options for atypical forms of Landau-Kleffner syndrome (LKS) are not well delineated. Many patients with typical LKS fail to respond to antiepileptic drug treatment, but some benefit from multiple subpial transections (MSTs). The authors report seven patients with autism or autistic epileptiform regression who responded in varying degrees to MSTs after failed medical management. These patients derived from an original cohort of 36 children (29 males, seven females, ranging from 2 years, 3 months to 11 years, 3 months, mean age = 5 years, 8 months) with a history of language delay or regression, as well as varying degrees of social and behavioral abnormalities, who were evaluated with video-electroencephalogram (EEG) monitoring over a 2-year period. Fifteen patients had clinical seizures (11 of the 19 children with autistic epileptiform regression and four of 12 autistic children). Epilepsy was refractory to medication in seven.

Surgical treatment variously involved MSTs of the left neocortex in temporal, parietal, and frontal regions, often including regions within the classic perisylvian language areas. One patient also had a left temporal lobectomy. In all seven patients, seizure control or EEG improved after MSTs. Language, social, and overall behavior improved to a moderate degree, although improvements were temporary in most. Autistic epileptiform regression resembles LKS in that both may respond to MST. MST is used to treat epilepsy in eloquent regions. The responsiveness of autistic epileptiform regression to MST buttresses the argument that autistic epileptiform regression is a form of focal epilepsy.

4.1.123. Bolman, W.M., Richmond, J.A. "A double-blind, placebo-controlled, crossover pilot trial of low dose dimethylglycine in patients with autistic disorder." *J Autism Dev Disord* 1999 Jun;29(3):191-4. Publication Types: Clinical Trial.

As the treatability of the syndrome of autism becomes more possible there is a great deal more interest in the effectiveness of various therapies. Although the very influential nonmedical literature cited in the Autism Research Review International Newsletter finds that dimethylglycine (DMG) is regarded as more effective than the usual psychopharmacologic drugs, there have been no studies of DMG using the currently accepted research methodology. We report a double-blind, placebo-controlled, crossover pilot study of low dose DMG and placebo in a sample of eight autistic males ranging in age from 4 years 5 months to 30 years 8 months, who completed the full 3 1/2-month study consisting of drug-free baseline periods at the beginning, end, and in-between two, 1-month double-blind trials in which DMG or placebo was given. Measures included the Campbell-NIMH rating scale, an experimental rating scale, and an individualized scale created for each child. Analysis of all three scales revealed no statistically significant differences, and parent reports were equally distributed. The major methodologic weaknesses of the study are thought to be the low dosage of DMG and the small sample size.

4.1.124. Cazzullo, A.G., Musetti, M.C., Musetti, L.; Bajo, S., Sacerdote, P., Panerai, A. "Beta-endorphin levels in peripheral blood mononuclear cells and long-term naltrexone treatment in autistic children." *Eur Neuropsychopharmacol* 1999 Jun;9(4):361-6.

Institute of Child and Adolescent Neurologic and Psychiatric Sciences, University of Milan, Italy.

We assessed the clinical and biological effects of high-dose, long-term Naltrexone (NTX) treatment in 11 children (3-11 years), who had been diagnosed as autistic. The drug was given following an open design, for 12 weeks. Beta-Endorphin (beta-END) was assayed in peripheral blood mononuclear cells after 1 and 3 months of treatment, and 6 months after the completion of the course. Baseline beta-END levels were higher than in healthy age-matched controls. In seven patients treatment reduced beta-END, whose levels rose in four

children. Autistic symptoms were considerably attenuated in all cases, with functional improvements involving several areas. There was a close correlation between the reduction in beta-END levels and the decrease of social withdrawal, and an evident—though weak—correlation between increases in beta-END and decreases in stereotypy and abnormal speech. Both effects persisted after treatment stopped.

4.1.125. Martin, A., Scahill, L., Klin, A., Volkmar, F.R. "Higher-functioning pervasive developmental disorders: rates and patterns of psychotropic drug use." *J Am Acad Child Adolesc Psychiatry* 1999 Jul;38(7):923-31.

Child Study Center, Yale University School of Medicine, New Haven, CT, USA. andres.martin@yale.edu

OBJECTIVE: To explore the frequency, characteristics, and associated target symptoms of psychotropic drug use among subjects with higher-functioning pervasive developmental disorders (HFPDDs). **METHOD:** A total of 109 children, adolescents, and adults (mean age = 13.9 years, SD = 6.9) consecutively seeking enrollment into the Yale Child Study Center's Project on Social Learning Disabilities were included in the study. Individuals in whom Asperger's disorder, autism, or pervasive developmental disorder-not otherwise specified had been previously diagnosed and who had a documented Full Scale IQ > or = 70 completed surveys on demographic, clinical, and medication history information. To naturalistically evaluate medication use patterns in this population, each drug class was analyzed with respect to demographic and clinical variables. **RESULTS:** In all, 55% of subjects were taking psychotropics, with 29.3% taking 2 or more medications simultaneously. Antidepressants were the most commonly used agents (32.1%), followed by stimulants (20.2%) and neuroleptics (16.5%). The clinical presentation of subjects taking psychotropic agents was heterogeneous, and most consistently included anxiety-related target symptoms (in 65% of medicated individuals). **CONCLUSIONS:** Psychotropic medication use appears to be common among subjects with HFPDDs, yet not generally based on the results of empirical research. Clinical heterogeneity among treated subjects suggests that psychiatric comorbidity may be overlooked in this population.

4.1.126. Hagopian, L.P., Thompson, R.H. "Reinforcement of compliance with respiratory treatment in a child with cystic fibrosis." *J Appl Behav Anal* 1999 Summer;32(2):233-6.

Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, Maryland 21205, USA.

An 8-year-old boy with cystic fibrosis (CF), mental retardation, and autism exhibited noncompliance with respiratory treatments that were essential for the management of his CF. A treatment involving shaping cooperation while still allowing escape for aggression and avoidance behavior resulted in increases compliance with respiratory treatments and decreases in problem behavior. Treatment gains were maintained over 3 months.

4.1.127. Scahill, L., Koenig, K. "Pharmacotherapy in children and adolescents with pervasive developmental disorders." *J Child Adolesc Psychiatr Nurs* 1999 Jan-Mar;12(1):41-3. Publication Types: Review, Review, Tutorial.

Yale Child Study Center, New Haven, CT, USA.

Children with autism and the related PDDs may benefit from serotonin reuptake inhibitors such as clomipramine, fluoxetine, fluvoxamine, and sertraline for targeting repetitive thoughts and behaviors, anxiety, and depressed mood. To date, however, there are few controlled studies of these agents in children with PDD, so definitive evidence is lacking. Despite preliminary results in favor of naltrexone, neuroleptic medication appears to be effective for reducing aggression, self-injurious behavior, agitation, and stereotypies. The primary drawback with traditional neuroleptics is risk of short- and long-term side effects. The newer atypical neuroleptics have the potential for benefit with fewer extrapyramidal side effects, but more study is needed to establish their efficacy and safety. Children on neuroleptic medications should be started at the lowest possible dose, with gradual increases until clinical benefit is observed. The likelihood of untoward side effects is increased if the medication dose is increased rapidly. Baseline measurement of target behaviors can be aided by using standardized scales. The presence of abnormal movements should be assessed before initiating treatment and at regular intervals during the course of treatment—including after medication withdrawal. Weight gain is emerging as a recurrent side effect with the atypical neuroleptics. Thus, weight should be monitored, and the family should be advised about a diet baseline. As with all treatments of children with severe behavioral difficulties, pharmacotherapy should be instituted in the context of an integrated treatment plan.

4.1.128. Feldman, H.M., Kolmen, B.K., Gonzaga, A.M. "Naltrexone and communication skills in young children with autism." *J Am Acad Child Adolesc Psychiatry* 1999 May;38(5):587-93. Publication Types: Clinical Trial, Randomized Controlled Trial.

Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, PA 15213, USA.

OBJECTIVE: To evaluate the effect of naltrexone on communication skills of young children with autism. **METHOD:** Twenty-four children with autism, 3.0 to 8.3 years old (mean 5.1) who were living at home and attending appropriate school programs, participated in a randomized, double-blind, placebo-controlled, crossover trial. Naltrexone, 1.0 mg/kg, or placebo was administered daily for 2 weeks. Communication was evaluated from videotaped samples of seminaturalistic parent-child interaction. Child and parent language were assessed using similar measures. **RESULTS:** In this heterogeneous sample, the median number of words the child produced on placebo was 9.5 (range 0-124). The median proportion of utterances with echolalia was 0.16. No differences were found between the naltrexone and placebo conditions in any of the measures of children or parents' communication. Significant correlations were found between

the child's number of words and developmental quotient (Spearman rho = 0.58, p = .003) and between the child's and parent's number of words (rho = 0.55, p = .005). **CONCLUSIONS:** Previous studies showed that naltrexone was associated with modest reduction in hyperactivity and restlessness in this group of children with autism. In this short-term study, the medication did not lead to improvement in communication, a core deficit of autism.

4.1.129. Riddle, M.A., Bernstein, G.A., Cook, E.H., Leonard, H.L., March, J.S., Swanson, J.M. "Anxiolytics, adrenergic agents, and naltrexone." *J Am Acad Child Adolesc Psychiatry* 1999 May;38(5):546-56. Publication Types: Review, Review, Tutorial.

Division of Child and Adolescent Psychiatry, Johns Hopkins Medical Institutions, Baltimore, MD, USA.

OBJECTIVE: To review extant data on the efficacy and safety of anxiolytic medications (benzodiazepines, buspirone, and other serotonin 1A agonists), adrenergic agents (beta-blockers and alpha 2-adrenergic agonists clonidine and guanfacine), and the opiate antagonist naltrexone that have been used to treat various psychopathologies in children and adolescents. To identify critical gaps in our current knowledge about these agents and needs for further research. **METHOD:** All available controlled trials of these medications in children and adolescents published in English through 1997 were reviewed. In addition, selected uncontrolled studies are included. **RESULTS:** The major finding, that there are virtually no controlled data that support the efficacy of most of these drugs for the treatment of psychiatric disorders in children and adolescents, is both surprising and unfortunate. For some drugs, e.g., buspirone and guanfacine, this is because no controlled studies have been carried out in children and/or adolescents. For other drugs, e.g., clonidine and naltrexone, most of the placebo-controlled studies have failed to demonstrate efficacy. **CONCLUSIONS:** The strongest recommendations for controlled studies of safety and efficacy in children and adolescents can be given for the following drugs: benzodiazepines for acute anxiety; buspirone (and newer serotonin 1A agonists as they become available) for anxiety and depression; beta-blockers for aggressive dyscontrol; guanfacine for attention-deficit/hyperactivity disorder; and naltrexone for hyperactivity, inattention, and aggression in autistic disorder.

4.1.130. Connolly, A.M., Chez, M.G., Pestronk, A., Arnold, S.T., Mehta, S., Deuel, R.K. "Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders." *J Pediatr* 1999 May;134(5):607-13.

Departments of Neurology and Pediatrics, Washington University, St. Louis Children's Hospital, St Louis, Missouri, USA.

OBJECTIVE: Etiologically unexplained disorders of language and social development have often been reported to improve in patients treated with immune-modulating regimens. Here we determined the frequency of autoantibodies to brain among such children. **DESIGN:** We collected sera from a cohort of

children with (1) pure Landau-Kleffner syndrome (n = 2), (2) Landau-Kleffner syndrome variant (LKSV, n = 11), and (3) autistic spectrum disorder (ASD, n = 11). None had received immune-modulating treatment before the serum sample was obtained. Control sera (n = 71) were from 29 healthy children, 22 with non-neurologic illnesses (NNIs), and 20 children with other neurologic disorders (ONDs). We identified brain autoantibodies by immunostaining of human temporal cortex and antinuclear autoantibodies using commercially available kits. **RESULTS:** IgG anti-brain autoantibodies were present in 45% of sera from children with LKSV, 27% with ASD, and 10% with ONDs compared with 2% from healthy children and control children with NNIs. IgM autoantibodies were present in 36% of sera from children with ASD, 9% with LKSV, and 15% with ONDs compared with 0% of control sera. Labeling studies identified one antigenic target to be endothelial cells. Antinuclear antibodies with titers $\geq 1:80$ were more common in children with ASD and control children with ONDs. **CONCLUSION:** Children with LKSV and ASD have a greater frequency of serum antibodies to brain endothelial cells and to nuclei than children with NNIs or healthy children. The presence of these antibodies raises the possibility that autoimmunity plays a role in the pathogenesis of language and social developmental abnormalities in a subset of children with these disorders.

4.1.131. Potenza, M.N., Holmes, J.P., Kanes, S.J., McDougle, C.J. "Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study." *J Clin Psychopharmacol* 1999 Feb;19(1):37-44. Publication Types: Clinical Trial.

Connecticut Mental Health Center, Department of Psychiatry, Yale University School of Medicine, New Haven, USA.

This pilot study examined the efficacy and tolerability of olanzapine in the treatment of children, adolescents, and adults with pervasive developmental disorders (PDDs). Eight patients with principal diagnoses (DSM-IV) of autistic disorder (N = 5) or PDD not otherwise specified (N = 3) were given olanzapine in an open-label, prospective fashion for 12 weeks. Clinical ratings were obtained at baseline and at the end of weeks (EOWs) 4, 8, and 12. Seven of eight patients completed the 12-week trial, and six of the completers were

deemed clinical responders as measured by ratings at the EOW 12 of "much improved" or "very much improved" on the global improvement item of the Clinical Global Impression Scale. Significant improvements in overall symptoms of autism, motor restlessness or hyperactivity, social relatedness, affectual reactions, sensory responses, language usage, self-injurious behavior, aggression, irritability or anger, anxiety, and depression were observed. Significant changes in repetitive behaviors were not observed for the group. The EOW 12 mean \pm SD daily dose of olanzapine was 7.8 \pm 4.7 mg/day. The drug was well tolerated with the most significant adverse effects noted to be increased appetite and weight gain in six patients and sedation in three. With respect to weight gain, the mean \pm SD weight for the group increased from 137.50 \pm 55.81 pounds (62.50 \pm 25.37 kilograms) at baseline to 155.94 \pm 55.13 pounds (70.88 \pm 25.06 kilograms) at EOW 12. No evidence of extrapyramidal side effects or liver function abnormalities was seen. These preliminary results suggest that olanzapine may be an effective and well tolerated drug in targeting core and related symptoms of PDDs in children, adolescents, and adults. Further studies, particularly those that are placebo-controlled and double-blinded, are indicated to better define the clinical use of olanzapine in these patient populations.

4.1.132. Rainey, L., van der Walt, J.H. "The anaesthetic management of autistic children." *Anaesth Intensive Care* 1998 Dec;26(6):682-6.

Department of Paediatric Anaesthesia, Women's and Children's Hospital, Adelaide, South Australia.

Autistic children are difficult to manage and there are no anaesthesia studies to suggest management strategies. We present five case reports which describe an integrated management program taking into account the special needs of autistic children and their families. We describe a method of early warning and recognition of these patients and the establishment of a database to allow review of our program. We also present a process to minimize the stress and problems inherent in the conventional admission process. Oral ketamine (6 to 7 mg/kg) has proven to be the most reliable preoperative sedative for these patients.

MANAGEMENT

Diet

4.2.1. Evangelidou, A., Vlachonikolis, I., Mihailidou, H., Spilioti, M., Skarpalezou, A., Makaronas, N., Prokopiou, A., Christodoulou, P., Liapi-Adamidou, G., Helidonis, E., Sbyrakis, S., Smeitink, J. "Application of a ketogenic diet in children with autistic behavior: pilot study." *J Child Neurol*. 2003 Feb;18(2):113-8. Publication Types: Clinical Trial.

Department of Paediatrics, Medical School, University of Crete, Crete, Greece. evangeli@med.uoc.gr

A pilot prospective follow-up study of the role of the ketogenic diet was carried out on 30 children, aged between 4 and 10 years, with autistic behavior. The diet was applied for 6 months, with continuous administration for 4 weeks, interrupted by 2-week diet-free intervals. Seven patients could not tolerate the diet, whereas five other patients adhered to the diet for 1 to 2 months and then discontinued it. Of the remaining group who adhered to the diet, 18 of 30 children (60%), improvement was recorded in several parameters and in accordance with the Childhood Autism Rating Scale. Significant improvement (> 12 units of the Childhood Autism Rating Scale) was recorded in two patients (pre-Scale: 35.00 \pm 1.41 [mean \pm SD]), average improvement (> 8 -12 units) in eight patients (pre-Scale: 41.88 \pm 3.14 [mean \pm SD]), and minor improvement (2-8 units) in eight patients (pre-Scale: 45.25 \pm 2.76 [mean \pm SD]). Although these data are very preliminary, there is some evidence that the ketogenic diet may be used in autistic behavior as an additional or alternative therapy.

4.2.2. Nye, C., Brice, A. "Combined vitamin B6-magnesium treatment in autism spectrum disorder." *Cochrane Database Syst Rev*. 2002;(4):CD003497. Publication Types: Meta-Analysis, Review, Review, Academic.

UCF Center for Autism & Related Disabilities, 12001 Science Dr, Suite 145, Orlando, Florida 32826, USA. cnye@mail.ucf.edu

BACKGROUND: The use of mega-vitamin intervention began in the early 1950's with the treatment of schizophrenic patients. Pyridoxine (vitamin B6) was first used with children diagnosed with "autism syndrome" when speech and language improvement was observed in some children as a result of large doses of B6. A number of published studies attempted to assess the effects of vitamin B6-Mg (Mg was found to reduce undesirable side effects from B6) on a variety of characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism. **OBJECTIVES:** To determine the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication and behavioural responses of children and adults with autism. **SEARCH STRATEGY:** We searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 2, 2002), MEDLINE (1966- January 2002), EMBASE (1980-January 2002), PsychINFO (1887 - January 2002), Dissertation Abstracts International (1861 - January 2002). The search engine FirstSearch was also used (January 2002). Reference lists for all the obtained studies and other review articles were examined for additional studies. **SELECTION CRITERIA:** All studies in which the participants

were randomly allocated prior to intervention and in which outcomes were compared to either a placebo or non-treated group were included. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently evaluated all potential studies identified as indicated above for inclusion. **MAIN RESULTS:** Two trials were included in the review. Both studies used a double-blind crossover design. One study (Tolbert 1993) provided insufficient data to conduct an analysis. The senior author was contacted for supporting data but was unable to provide the needed information. The remaining study (Findling, 1997) yielded no significant differences between treatment and placebo group performances following the B6 intervention on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. **REVIEWER'S CONCLUSIONS:** Due to the small number of studies, the methodological quality of studies, and small sample sizes, no recommendation can be advanced regarding the use of B6-Mg as a treatment for autism.

4.2.3. Piazza, C.C., Patel, M.R., Santana, C.M., Goh, H.L., Delia, M.D., Lancaster, B.M. "An evaluation of simultaneous and sequential presentation of preferred and nonpreferred food to treat food selectivity." *J Appl Behav Anal* 2002 Fall;35(3):259-70.

Marcus Institute, Atlanta, Georgia 30329, USA.

In the current investigation, we compared two methods of food presentation (simultaneous vs. sequential) to increase consumption of nonpreferred food for 3 children with food selectivity. In the simultaneous condition, preferred foods were presented at the same time as nonpreferred food (e.g., a piece of broccoli was presented on a chip). In the sequential condition, acceptance of the nonpreferred food resulted in presentation of the preferred food. Increases in consumption occurred immediately during the simultaneous condition for 2 of the 3 participants. For 1 participant, increases in consumption occurred in the simultaneous condition relative to the sequential condition, but only after physical guidance and re-presentation were added to treatment. Finally, consumption increased for 1 participant in the sequential condition, but only after several sessions. These results are discussed in terms of possible mechanisms that may alter preferences for food (i.e., establishing operations, flavor-flavor conditioning).

4.2.4. Knivsberg, A.M., Reichelt, K.L., Høien, T., Nodland, M. "A randomised, controlled study of dietary intervention in autistic syndromes." *Nutr Neurosci* 2002 Sep;5(4):251-61. Publication Types: Clinical Trial, Randomized Controlled Trial.

Center for Reading Research, Stavanger University College, Norway. ann-mari.knivsberg@slf.his.no

Impaired social interaction, communication and imaginative skills characterize autistic syndromes. In these syndromes urinary peptide abnormalities, derived from gluten, gliadin, and casein, are reported. They reflect processes with opioid effect. The aim of this single blind study was to evaluate effect of gluten and casein-free diet for children with autistic

syndromes and urinary peptide abnormalities. A randomly selected diet and control group with 10 children in each group participated. Observations and tests were done before and after a period of 1 year. The development for the group of children on diet was significantly better than for the controls.

4.2.5. Cornish, E. "Gluten and casein free diets in autism: a study of the effects on food choice and nutrition." *J Hum Nutr Diet* 2002 Aug;15(4):261-9.

Community Nutrition Service, South Derbyshire Community Health NHS Trust, Dar es Salaam, Tanzania.

BACKGROUND: There is growing interest in possible dietary involvement in the aetiology and treatment of Autistic Spectrum Disorders (ASD). Research has focused on the physiological and behavioural effects of dietary change but has not examined the effect of exclusion diets on nutritional intake. **AIMS:** The aim of this study was to examine whether the removal of major dietary staples placed children with autism at risk of nutrient deficiency and compares their food choice with ASD children not following gluten and/or casein free diets. **METHODS:** A postal questionnaire was sent to parents of children aged 3-16 years, diagnosed with ASD belonging to the National Autistic Society in Leicestershire and southern Derbyshire. Detailed dietary information and a 3-day food diary were collected. The sample size was small: those using gluten/casein free diets (n = 8) and those not following diet (n = 29). **RESULTS:** Nutrient intakes fell below the Lower Reference Nutrient Intake (LRNI) in 12 children (32%) for zinc, calcium, iron, vitamin A, vitamin B12 and riboflavin in the nondiet group and four children (50%) for zinc and calcium in the diet group. Fruit and vegetable intakes were higher and cereal, bread and potato consumption were lower in those children using gluten and/or casein free diets. **CONCLUSION:** No significant differences in the energy, protein and micronutrient intakes were found between the two groups of children. A longitudinal prospective study is suggested to examine whether differences in food choice are the result of dietary intervention or the prerequisite for the successful application of diet in this special group of children.

4.2.6. Bowers, L. "An audit of referrals of children with autistic spectrum disorder to the dietetic service." *J Hum Nutr Diet* 2002 Apr;15(2):141-4.

Llanfrechfa Grange Hospital, Gwent Healthcare NHS Trust, Cwmbran, UK. sue.cullen@gwent.wales.nhs.uk

Autistic spectrum disorder (ASD) is a developing area for dietetic referrals. There is little published data on current dietetic practice. Some children with ASD are referred for gluten/casein free diet. The theory is that abnormal metabolites in the urine may be a result of incomplete breakdown of gluten and casein in the gut. There are some published open studies that support the efficiency of such a diet [Knivsberg et al. (1995) *Scand. J. Educ. Res.*39: 223; Lucarelli et al. (1995) *Panminerva Med.*37: 137; Whiteley et al. (1999) *Int. J. Res. Practice* 3: 45] and also that there are many anecdotal reports that the diet helps some children. **AIMS AND OBJECTIVES:** This study aimed to audit the types of referral made to the

dietetic service to identify key dietetic issues and to describe factors which may influence outcome/disease management. **METHODS:** Dietetic records were used to audit the referrals to the dietetic service over a 3-month period. Seven-day diet histories were assessed using computer food composition tables and topics of interest recorded against a draft protocol agreed within the profession. **RESULTS:** Requests for gluten-free and casein-free dietetic advice, and/or the management of food selectivity and dysfunctional feeding behaviour constituted the majority of referrals. In many cases, child's environment was rarely simple. **CONCLUSIONS:** Despite the limitations of this small study, the findings suggest that the management of these referrals is highly complex. A dietitian's input should ensure that the nutritional adequacy of the diet is maintained or restored.

4.2.7. Mc Clannahan, L.E., Mac Duff, G.S., Krantz, P.J. "Behavior analysis and intervention for adults with autism." *Behav Modif* 2002 Jan;26(1):9-26. Publication Types: Evaluations Studies,

Princeton Child Development Institute, USA.

This article describes a behavioral intervention program for adults with autism, suggests that preparation for adulthood should begin in early childhood, asserts that the curriculum should be just as comprehensive and evaluation criteria just as rigorous in programs for adults as in programs for children, and proposes that close examination of adult's repertoires may lead to key modifications of services delivered to children. Along the way, the authors provide some data on the progress of 15 people who are now adults and whom they have known for 15 to deficits displayed by adults with autism, a program model that prevents "falling through the cracks" must provide an array of options - from training centre to supported employment.

4.2.8. Green, G., Brennan, L.C., Fein, D. "Intensive Behavioral treatment for a toddler at high risk for autism." *Behav Modif* 2002 Jan; 26(1) : 69-102.

New England Centre for Children, University of Massachusetts, USA.

Intensive, comprehensive treatment using a variety of applied behavior analysis methods was provided to a toddler who was determined to be at high risk for autism at the age of about 1 year. Initially, treatment was delivered in a one-to-one adult-child format in the child's home and other settings, with gradual transitions to group instruction in early intervention and preschool classrooms. Intensive treatment continued for 3 years; by the 4th year, the child was spending most of her time in a regular preschool classroom, with minimal ongoing one-to-one instruction. Direct observations data and results of norm-referenced tests documented large increases in language, social, cognitive, and daily living skills over the course of treatment. After 4 years, the child demonstrated no behavioral norm-referenced tests of cognitive and language skills, and was functioning as a typical child a regular public school kindergarten classroom.

4.2.9. Eikesth, S., Smith, T., Jahr, E., Eldevik, S. **"Intensive behavioral treatment at school for 4-to 7-years-old children with autism. A 1-year comparison controlled study."** *Behav Modif* 2002 Jan;26(1) : 49-68. Publication Types: Clinical Trial. Akershus College.

This study was designed to evaluate 1 year of intensive treatment for 4-to 7-year-old children with autism. An independent clinician assigned children to either behavioral treatment (n=13) or eclectic treatment (n=12). Assignment was based on availability of personnel to supervise treatment and was not influenced by child characteristics or family preference. The two treatment groups received similar amounts of treatment (M=28.52 hours per week at the child's school). Children in the behavioral treatment group made significantly larger gains on standardized tests than did children in the eclectic treatment group. Results suggest that some 4-to 7-year-olds may make large gains with intensive behavioral treatment, that such treatment can be successfully implemented in school settings, and that specific aspects of behavioral treatment (not just its intensity) may account for favorable outcomes.

4.2.10. Knivsber, A.M., Reichelt, K.L., Nodland, M. **"Reports on dietary intervention in autistic disorders."** *Nutr Neurosci* 2001;4(1):25-37. Publication Types: Review, Review, Tutorial.

Center for Reading Research, Stavanger College, Norway ann-mari.knivsberg@slf.his.no

Autism is a developmental disorder for which no cure currently exists. Gluten and/or casein free diet has been implemented to reduce autistic behaviour, in addition to special education, since early in the eighties. Over the last twelve years various studies on this dietary intervention have been published in addition to anecdotal, parental reports. The scientific studies include both groups of participants as well as single cases, and beneficial results are reported in all, but one study. While some studies are based on urinary peptide abnormalities, others are not. The reported results are, however, more or less identical; reduction of autistic behaviour, increased social and communicative skills, and reappearance of autistic traits after the diet has been broken.

4.2.11. Ahearn, W.H., Castine, T., Nault, K., Green, G. **"An assesment of food acceptance in children with autism or pervasive developmental disorder-not otherwise specified."** *J Autism Dev Disord* 2001 Oct;31(5): 505-11.

The New England Centre for Children, Southboro, MA 01772-2108, USA. Bahearn@necc.org

Some children with autism and pervasive developmental disorder-not otherwise specified (PDD - NOS) have been reported to have atypical feeding behavior, such as sensitivity to food texture and selective preferences for particular foods. No systematic studies of feeding behavior in this population have been published. Munk and Repp (1994) developed methods for assessing feeding problems in individuals with cognitive and physical disabilities that allow categorization of individual feeding patterns based on responses to repeated

presentations of food. In this Study, we systematically replicated the Munk and Repp procedures with children with autism and PDD - NOS. Thirty children, ages 3 to 14 years, were exposed to 12 food items across 6 sessions. Food acceptance, food expulsion, and disruptive behavior were recorded on a trial - by - trial basis. Approximately half of the participants exhibited patterns of food acceptance, indicating selectivity by food category of food texture. Others consistently accepted or rejected items across food categories. Whether these patterns of food acceptance are typical remains to be determined by comparison with the feeding patterns of typically developing children and other children with developmental delays.

4.2.12. Deleon, I.G., Neidert, P.L., Anders, B.M., Rodriguez-Catter, V. **"Choices between positive and negative reinforcement during treatment for escape - maintained behavior."** *J Appl Behav Anal* 2001 Winter; 34(4):521-5. Publication Types: Clinical Trial.

Neurobehavioral Unit Kennedy Krieger Institute, Baltimore, Maryland 21205, USA. deleon@kennedykrieger.org

Positive reinforcement was more effective than negative reinforcement in promoting compliance and reducing escape - maintained problem behavior for a child with autism. Escape extinction was then added while the child was given a choice between positive or negative reinforcement for compliance and the reinforcement schedule was thinned. When the reinforcement requirement reached 10 consecutive tasks, the treatment effects became inconsistent and reinforcer selection shifted from a strong preference for positive reinforcement to an unstable selection pattern.

4.2.13. Dixon, M.R., Cummings, A. **"Self-control in children with autism: response allocation during delays to reinforcement."** *J Appl Behav Anal* 2001 Winter; 34(4): 491-5. Publication Types: Clinical Trial.

Behavior Analysis and Therapy Program, Rehabilitation Institute, Southern Illinois University, Carbondale 62901, USA. mdixon@siu.edu

This study examined the use of progressive - delay schedule of reinforcement to increase self-control and decrease disruptive behavior in children with autism. When initially given the choice between an immediate smaller reinforcer and a larger delayed reinforcer, all participants chose the smaller reinforcer. When access to the larger reinforcer required either no activity or engaging in a concurrent task during the delay, all participants demonstrated both self-control and preference for a response requirement. Disruptive behavior decreased during delays that required concurrent task compared to sessions without an activity requirement.

4.2.14. Boyd, R.D., Corley, M.J. **"Outcome survey of early intensive behavioral intervention for young children with autism in a community setting."** *Autism* 2001 Dec; 5(4): 430-41.

Golden Gate Regional Centre, San Francisco, CA, USA.

This article presents findings from an outcome survey of the effects of early intensive behavioral intervention (EIBI) for young children with autism in a community setting. Results from both individual case reviews and parent questionnaires are presented, with the data failing to support an instances of recovery while still yielding a high degree of parental satisfaction with the treatment. Moreover, a follow-up inquiry into the type of services each child was receiving in his or her post-EIBI setting documents continued dependence on extensive educational and related developmental services, suggesting that the promise of future treatment sparing did not materialize. Limitations of the survey in evaluating community-based EIBI services are discussed along with the need for further research designed to document the effectiveness of services provided to young children with ASD in the community.

4.2.15. Mullins, J.L., Christian, L. "The effects of progressive relaxation training on the disruptive behavior of a boy with autism." *Res Dev Disabil* 2001 Nov-Dec;22(6): 449-62.

University of Kansas, USA.

This Study examined the effects of progressive relaxation training on the disruptive behaviors of a boy with autism. Moreover, his overt relaxed behaviors before and after relaxation training were measured using the Behavioral Relaxation Scale (Poppen, 1988, Poppen, 1998). After the participant received training in progressive relaxation procedures in multielement design with three conditions was utilized to determine the effects of the procedures on the duration of the boy's disruptive behaviors during leisure activity sessions. The conditions were (a) relaxation prior to a leisure activity session, which represented a baseline condition. Results indicated that the participant acquired progressive relaxation skills, displayed more relaxed behaviors after performing the procedures, and showed a decrease in the duration of his disruptive behaviors upon completing progressive relaxation training prior to a leisure activity session. Implications for future research are discussed.

4.2.16. Weiskop, S., Matthews, J., Richdale, A. "Treatment of sleep problems in a 5-year-old boy with autism using behavioural principles." *Autism* 2001 Jun;5(2): 209-21.

RMIT University, Bundoora, Victoria, Australia.

This article presents a case study which is part of a larger project on sleep problems in children with autism. The successful treatment of sleep problems (night settling, night walking, and co-sleeping) in a boy of 5 years 4 months with autism is described. The intervention was based on behavioural principles and involved the parents attending an individually-run parent training programme. The Programme consisted of an interview, three weekly training sessions and a review session. The parents learned how to use a bedtime routine, reinforcement, effective instructions, partner support strategies and extinction procedures. Once the techniques were implemented, the child learned how to settle himself to bed and how to sleep alone for the entire night. For this child, the results of the sleep programme were clinically significant

as measured by a scale of goal achievement, and were maintained at a 3 month and a 12 month follow-up.

4.2.17. Dozier, C.L., Carr, J.E., Enlof, K., Landaburu, H., Eastridge, D., Kellum, K.K. "Using fixed-time schedules to maintain behavior: a preliminary investigation." *J Appl Behav Anal* 2001 Fall;34(3):337-40. Publication Types: Evaluation Studies.

University of Nevada, Reno, USA. cld@ufl.edu

The purpose of this study was to evaluate the potential of fixed-time (FT) schedules to maintain behavior. Two children who had been diagnosed with autism were taught a functional task. Subsequently, three different FT schedules (i.e., yoked, thin, dense) were compared to determine their capacity to maintain task responding. Results suggested that FT schedules may be used to maintain previously acquired behavior.

4.2.18. Brudnak, M.A. "Application of genomeceuticals to the molecular and immunological aspects of autism." *Med Hypotheses* 2001 Aug;57(2):186-91.

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Autism is a developmental disease affecting as many as 1 in 300 children and is often characterized as a mental disorder originating in infancy that is associated with self-absorption, inability to interact socially, behavior, and language dysfunction (e.g. echolalia). Current theories indicate an important role of diet in the development of disease. It is thought that, as a result of maldigestion of casein and gluten, opioid-type peptides, or exorphins, are produced. Additionally, because of the time-frame of development of the disease, there has been an association with childhood vaccination. Consequently, prevailing therapies attempt to address these causes in one, or a combination, of three ways: diet restriction (removing casein and gluten); supplementation with exogenous enzymes; and probiotic bacteria. Until recently, none of the therapies addressed the molecular mechanisms that may be at work in the development and progression of autism. This paper presents potential molecular and cellular mechanism related to autism as well as discusses their application to the treatment of the disease through the application of genomeceuticals. Additionally, a link between developmentally associated aberrant immune and inflammatory responses, and autism is suggested and explored. Copyright 2001 Harcourt Publishers Ltd.

4.2.19. Levin, L., Carr, E.G. "Food selectivity and problem behavior in children with developmental disabilities. Analysis and intervention." *Behav Modif* 2001 Jul;25(3):443-70.

State University of New York at Stony Brook and Developmental Disabilities Institute, USA.

Excessive food selectivity typifies some children with developmental disabilities. We conducted functional analyses to determine the controlling variables for problem behavior that accompanied food selectivity and analyzed the role of

establishing operations in ameliorating food selectivity. Specifically, we studied the differential effects on intervention efficacy of an individual's having or not having access to preferred food items prior to an intervention that involved the presence versus absence of a positive reinforcement contingency applied to food consumption. Participants displayed significantly more problem behavior during the nonpreferred-foods condition. Participants consumed nonpreferred target food items only when prior access to preferred foods was limited and a positive reinforcement contingency was implemented. Functional analysis suggested that problem behavior was maintained by negative reinforcement. Intervention data suggested that establishing operations increased the efficacy of the contingency-based intervention. The implications of applying this intervention in the community were discussed as were the relative merits of stimulus fading versus escape extinction intervention strategies.

4.2.20. Kern, J.K., Miller, V.S., Cauller, P.L., Kendall, P.R., Mehta, P.J., Dodd, M. "Effectiveness of N,N-dimethylglycine in autism and pervasive developmental disorder." *J Child Neurol* 2001 Mar;16(3):169-73. Publication Types: Clinical Trial, Randomized Controlled Trial.

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N,N-dimethylglycine, a dietary supplement, has been reported to be beneficial in children with autism and pervasive developmental disorder. We examined the effectiveness of dimethylglycine in children with autism and pervasive developmental disorder in a double-blind, placebo-controlled study. Thirty-seven children between 3 and 11 years of age with a diagnosis of autism and/or pervasive developmental disorder were gender and age matched and randomly assigned to receive either placebo or dimethylglycine for 4 weeks. All children were assessed before and after treatment on two behavioral measures, the Vineland Maladaptive Behavior Domain and the Aberrant Behavior Checklist. Standardized neurologic examinations before and after treatment on 33 children showed no change. An overall improvement on all behavioral measures was observed for both the placebo and the dimethylglycine groups. However, the improvement among the children who received dimethylglycine was not statistically different from the improvement observed among the children who received the placebo. The children who participated in this study were a heterogeneous group, and their apparent responses to the dimethylglycine varied. Some children appeared to respond positively to the dimethylglycine, and there was a smaller proportion of negative changes in the dimethylglycine group, but the quantitative changes in the dimethylglycine behavioral assessments were not significantly different from what was observed among children who received placebo.

4.2.21. Fatemi, S.H., Halt, A.R., Stary, J.M., Realmuto, G.M., Jalali-Mousavi, M. "Reduction in anti-apoptotic protein Bcl-2 in autistic cerebellum." *Neuroreport* 2001 Apr 17;12(5):929-33.

Department of Psychiatry, University of Minnesota Medical School, Minneapolis 55455, USA.

Autism is a neurodevelopmental disorder with genetic and environmental etiologies. Neurohistologic findings have shown Purkinje cell depletion and atrophy in the cerebellum of autistic subjects. We hypothesized that apoptotic mechanisms might explain these Purkinje cell findings. Bcl-2 is a potent anti-apoptotic regulatory protein, which is reduced in schizophrenic brains. Autistic and normal control cerebellar cortices matched for age, sex and PMI were prepared for SDS-gel electrophoresis and Western blotting using specific anti-Bcl-2 antibodies. Quantification of Bcl-2 showed a significant 34-51% reduction in autistic cerebellum (mean (+/- s.d.) optical density/75 microg protein 0.290 +/- 0.08, n = 5) compared with controls (0.595 +/- 0.31, n = 8; p < 0.04); levels of neuronal-specific class III beta-tubulin (controls 49.8 +/- 6.7; autistics 36.2 +/- 18.2), or beta-actin (controls 7.3 +/- 2.7; autistics 6.77 +/- 0.66) in the same homogenates did not differ significantly between groups. These results indicate for the first time that autistic cerebellum may be vulnerable to pro-apoptotic stimuli and to neuronal atrophy as a consequence of decreased Bcl-2 levels.

4.2.22. Williams, P.G., Dalrymple, N., Neal, J. "Eating habits of children with autism." *Pediatr Nurs* 2000 May-Jun;26(3):259-64.

University of Louisville, Child Evaluation Center, Louisville, KY, USA.

Autism is a developmental disorder characterized by severe deficits in social interaction and communication, as well as by stereotyped and repetitive behaviors. Children with autism frequently have significant eating difficulties with highly restricted range of food choices. Eating habits and patterns are often unusual and have an impact on family life. The purpose of this article was to review pertinent information regarding this complex developmental disorder and describe a recent study based on a parent survey of feeding patterns in children with autism to give a new perspective for both parents and professionals.

4.2.23. Burd, L., Stenehjem, A., Franceschini, L.A., Kerbeshian, J. "A 15-year follow-up of a boy with pyridoxine (vitamin B6)-dependent seizures with autism, breath holding, and severe mental retardation." *J Child Neurol* 2000 Nov;15(11):763-5.

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Pyridoxine (vitamin B6) (2q31) dependency is a rare autosomal-recessive disorder that causes a severe seizure disorder of prenatal or neonatal onset. The abnormality appears to inhibit the binding of vitamin B6 to the enzyme glutamic acid decarboxylase-1, which is needed for the biosynthesis of gamma-aminobutyric acid (GABA). Most patients with pyridoxine-dependent seizures require lifelong treatment with pyridoxine. The full range of associated

symptomatology is unknown since fewer than 100 cases have been reported. A majority of cases are mentally retarded. We report a 15-year-old boy with pyridoxine-dependent seizures, nonpyridoxine-dependent seizures, severe mental retardation, autistic disorder, aerophagia, breath holding, and self-injury. This complex outcome should alert clinicians to the wide range of neuropsychiatric outcomes associated with this disorder.

4.2.24. Bell, J.G., Sargent, J.R., Tocher, D.R., Dick, J.R. "Red blood cell fatty acid compositions in a patient with autistic spectrum disorder: a characteristic abnormality in neurodevelopmental disorders?" *Prostaglandins Leukot Essent Fatty Acids* 2000 Jul-Aug;63(1-2):21-5. Publication Types: Review, Review, Tutorial.

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The fatty acid compositions of red blood cell (RBC) phospholipids from a patient with autistic spectrum disorder (ASD) had reduced percentages of highly unsaturated fatty acids (HUFA) compared to control samples. The percentage of HUFA in the RBC from the autistic patient was dramatically reduced (up to 70%) when the sample was stored for 6 weeks at -20 degrees C. However, only minor HUFA reductions were recorded in control samples stored similarly, or when the autistic sample was stored at -80 degrees C. A similar instability in RBC HUFA compositions upon storage at -20 degrees C has been recorded in schizophrenic patients. In a number of other neurodevelopmental conditions, including attention deficit hyperactivity disorder (ADHD) and dyslexia, reduced concentrations of RBC HUFA have been recorded. The extent and nature of these aberrations require further assessment to determine a possible common biochemical origin of neurodevelopmental disorders in general. To facilitate this, a large scale assessment of RBC fatty acid compositions in patients with ASD, and related disorders, should be performed as a matter of urgency. Supplementing cells in culture with the tryptophan metabolite indole acrylic acid (IAA) affected the levels of cellular HUFA and prostaglandin production. Indole acroyl glycine (IAG), a metabolite of IAA excreted in urine, is found in high concentrations in patients with neurodevelopmental disorders including ASD, ADHD, dyslexia, Asperger's syndrome and obsessive compulsive disorder. Copyright 2000 Harcourt Publishers Ltd.

4.2.25. Richardson, A.J., Ross, M.A. "Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum." *Prostaglandins Leukot Essent Fatty Acids* 2000 Jul-. Publication Types: Review, Review, Tutorial.

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There is increasing evidence that abnormalities of fatty acid and membrane phospholipid metabolism play a part in a wide range of neurodevelopmental and psychiatric disorders. This proposal is discussed here in relation to attention-deficit/hyperactivity disorder (ADHD), dyslexia, developmental coordination disorder (dyspraxia) and the autistic spectrum. These are among the most common neurodevelopmental disorders of childhood, with significant implications for society as well as for those directly affected. However, controversy still surrounds both the identification and management of these conditions, and while their aetiology is recognized as being complex and multifactorial, little progress has yet been made in elucidating predisposing factors at the biological level. An overview is provided here of the contents of this Special Issue, which contains a selection of reports from a unique multidisciplinary workshop involving both researchers and clinicians. Its purpose was to explore the possibility that ADHD, dyslexia, dyspraxia and autism fall within a phospholipid spectrum of disorders. This proposal could explain the high degree of co-morbidity between these conditions, their aggregation within families and relation to other psychiatric disorders, and a range of associated features that are already well known at a clinical level. The existing evidence for fatty acid abnormalities in these disorders is summarized, and new approaches are outlined that have the potential to improve both the identification and the management of these and related neurodevelopmental and psychiatric conditions. Copyright 2000 Harcourt Publishers Ltd.

4.2.26. Megson, M.N. "Is autism a G-alpha protein defect reversible with natural vitamin A?" *Med Hypotheses* 2000 Jun;54(6):979-83.

Pediatric and Adolescent Ability Center, Richmond, VA 23226, USA.

Autism may be a disorder linked to the disruption of the G-alpha protein, affecting retinoid receptors in the brain. A study of 60 autistic children suggests that autism may be caused by inserting a G-alpha protein defect, the pertussis toxin found in the DPT vaccine, into genetically at-risk children. This toxin separates the G-alpha protein from retinoid receptors. Those most at risk report a family history of at least one parent with a pre-existing G-alpha protein defect, including night blindness, pseudohypoparathyroidism or adenoma of the thyroid or pituitary gland. Natural vitamin A may reconnect the retinoid receptors critical for vision, sensory perception, language processing and attention. Autism spectrum disorders have increased from 1 in 10 000 in 1978 to 1 in 300 in some US communities in 1999. Recent evidence indicates that autism is a disorder of the nervous system and the immune system, affecting multiple metabolic pathways.

MANAGEMENT

Psychological

4.3.1. McDougle, C.J., Stigler, K.A., Posey, D.J. "Treatment of aggression in children and adolescents with autism and conduct disorder." *J Clin Psychiatry*. 2003;64 Suppl 4:16-25. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

The optimal clinical management of aggression in children and adolescents involves both behavioral and pharmacologic intervention strategies. This article reviews medication treatments for youngsters with autistic disorder and conduct disorder, conditions for which the pharmacologic management of aggression is often necessary. Efficacy results and associated adverse effects from selected clinical trials of most classes of psychotropic medications are discussed. While preliminary progress has been made in the development of medication treatments for these serious disorders of youth, additional controlled research and longitudinal studies are needed to better understand the efficacy and tolerability of currently available compounds within each diagnostic group.

4.3.2. Klin, A., Jones, W., Schultz, R., Volkmar, F. "The enactive mind, or from actions to cognition: lessons from autism." *Philos Trans R Soc Lond B Biol Sci*. 2003 Feb 28;358(1430):345-60. Publication Types: Review, Review Literature.

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Normative-IQ individuals with autism are capable of solving explicit social cognitive problems at a level that is not matched by their ability to meet the demands of everyday social situations. The magnitude of this discrepancy is now being documented through newer techniques such as eye tracking, which allows us to see and measure how individuals with autism search for meaning when presented with naturalistic social scenes. This paper offers an approach to social cognitive development intended to address the above discrepancy, which is considered a key element for any understanding of the pathophysiology of autism. This approach, called the enactive mind (EM), originates from the emerging work on 'embodied cognitive science', a neuroscience framework that views cognition as bodily experiences accrued as a result of an organism's adaptive actions upon salient aspects of the surrounding environment. The EM approach offers a developmental hypothesis of autism in which the process of acquisition of embodied social cognition is derailed early on, as a result of reduced salience of social stimuli and concomitant enactment of socially irrelevant aspects of the environment.

4.3.3. Mayes, S.D., Calhoun, S.L. "Ability profiles in children with autism: influence of age and IQ." *Autism*. 2003 Mar;7(1):65-80.

Penn State College of Medicine, USA.

To understand the effect of IQ and age on ability in children with autism, psychological data were analyzed for 164 3- to

15-year-olds with autism (IQs 14-143). As age increased, so did IQ, which probably reflects both an actual increase in IQ over time and the likelihood that brighter children are diagnosed later. Early in life, 67 percent had normal motor and delayed speech milestones. Verbal IQ continued to lag behind non-verbal IQ during the preschool years. By school age, the gap between verbal and non-verbal IQs had closed. Visual reasoning exceeded graphomotor scores for all children, and surpassed IQ for most. Graphomotor scores were significantly below IQ for both high-IQ groups. For school-age children with low IQs, math, spelling, and writing scores were consistent with IQ and reading was above IQ. School-age children with high IQs had average reading, math, and spelling scores and a weakness in writing.

4.3.4. Whalen, C., Schreibman, L. "Joint attention training for children with autism using behavior modification procedures." *J Child Psychol Psychiatry*. 2003 Mar;44(3):456-68. Publication Types: Clinical Trial, Controlled Clinical Trial.

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BACKGROUND: Deficits in joint attention are considered by many researchers to be an early predictor of childhood autism (e.g., Osterling & Dawson, 1994) and are considered to be pivotal to deficits in language, play, and social development in this population (Mundy, 1995). Although many researchers have noted the importance of joint attention deficits in the development of children with autism (e.g., Mundy, Sigman, & Kasari, 1994) and have called for intervention strategies (e.g., Mundy & Crowson, 1997), few studies have attempted to target joint attention. In this study, joint attention behaviors were taught to children with autism using a behavior modification procedure. **METHODS:** A multiple-baseline design was implemented to evaluate intervention effects. The following target behaviors were included in the intervention: 1) Responding to showing, pointing, and gaze shifting of adult; 2) Coordinated gaze shifting (i.e., coordinated joint attention); and 3) Pointing (with the purpose of sharing, not requesting). Generalization to setting and parent, follow-up sessions, and social validation measures were also analyzed. **RESULTS:** Joint attention behaviors were effectively trained and targeted behaviors generalized to other settings. In addition, positive changes were noted by naive observers using social validation measures. **CONCLUSIONS:** Integrating joint attention training into existing interventions may be important for children with autism. In addition, training parents in these techniques may help to maintain joint attention skills outside of the treatment setting.

4.3.5. Elder, J.H., Valcante, G., Won, D., Zylis, R. "Effects of in-home training for culturally diverse fathers of children with autism." *Issues Ment Health Nurs*. 2003 Apr-May;24(3):273-95.

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Recently there has been mounting interest in the role of fathers and the effect of their increasing involvement on child

development. However, to date, little has been reported regarding the role of fathers with developmentally delayed children (e.g., autism, pervasive developmental delays) and cultural influences on father-child interactions. In this article we address this knowledge gap by reporting four cases representing the major ethnic groups. For each case, we (1) define the concept of fatherhood in its cultural context, (2) review and summarize related father-child research, and (3) present findings from our study evaluating the effects of an in-home intervention for autistic children. While variability is noted within and among the culturally diverse father-child dyads, there are also similarities across ethnic groups. Results of this study are promising, demonstrating the value of single subject experimental methods in characterizing and beginning to understand complex father-child interactions in autism and related child psychiatric disorders.

4.3.6. Campbell, J.M. "Efficacy of behavioral interventions for reducing problem behavior in persons with autism: a quantitative synthesis of single-subject research." *Res Dev Disabil.* 2003 Mar-Apr;24(2):120-38. Publication Types: Meta-Analysis.

Department of Psychology, University of Memphis, Memphis, TN, USA. jcampbel@coe.uga.edu

The efficacy of behavioral interventions for problem behavior in persons with autism was reviewed. One hundred and seventeen published articles representing 181 individuals with autism were examined. Articles were selected from 15 journals. Participant, treatment, and experimental variables were evaluated. Three effect sizes were calculated for each article. Behavioral treatments are effective in reducing problematic behaviors in individuals with autism. Type of target behavior and type of treatment did not moderate the average effect of treatment. As measured by percentage of zero data (PZD), three variables were predictive of behavioral suppression beyond that accounted for by behavioral topography and treatment type. Reliability of observation and number of treatment data points were positively related to PZD scores. Treatments based on experimental functional analysis (EFA) produced higher average PZD scores than treatments that did not include an EFA. The implications of the findings, study limitations, and suggestions for future research are discussed.

4.3.7. Scattone, D., Wilczynski, S.M., Edwards, R.P., Rabian, B. "Decreasing disruptive behaviors of children with autism using social stories." *J Autism Dev Disord.* 2002 Dec;32(6):535-43.

Department of Pediatrics, Division of Child Development and Behavioral Medicine, University of Mississippi Medical Center, Jackson 39216-4505, USA. dscattone@ped.umsmed.edu

Few studies have been conducted in the area of social stories, and the limitations of these studies (i.e., improper story construction and methodological confounds) raise questions about effectiveness of social story interventions. This study examined the effectiveness of properly constructed social

stories that have been introduced into the natural environment to target the disruptive behavior of three children with autism. A multiple baseline design across participants was employed, and a decrease in disruptive behavior was evidenced when the intervention was implemented for all participants. Based on the results of the present research, future areas of investigation outlining the limitations and potential benefits of social stories were discussed.

4.3.8. Whitaker, P. "Supporting families of preschool children with autism: what parents want and what helps." *Autism.* 2002 Dec;6(4):411-26..

Leicestershire County Council, UK. philip.whitaker@virgin.net

This paper describes a local education authority project to provide support to the families of preschool children with autistic spectrum disorders. As part of an evaluation study, all parents were interviewed when their children entered full-time education and left the service's caseload. The report outlines key findings regarding levels of satisfaction with the service provided and describes parental responses to the different components of the support offered. All parents rated the input of the support worker as 'very useful'. Parents particularly valued the following: support to 'make sense' of their child's development and needs; practical strategies for facilitating language and engaging in interactive play; and support to the nurseries and playgroups attended by their children. The interviews also looked at parents' experience of diagnosis and their needs in the immediate aftermath. Key implications of these findings, and of this model of service delivery, are also discussed.

4.3.9. Horner, R.H., Carr, E.G., Strain, P.S., Todd, A.W., Reed, H.K. "Problem behavior interventions for young children with autism: a research synthesis." *J Autism Dev Disord.* 2002 Oct;32(5):423-46. Publication Types: Review, Review, Academic.

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This paper provides a summary of research on behavioral interventions for children with autism 8 years of age or younger published between 1996 and 2000. The analysis is divided into four sections: (1) emerging themes in the technology of behavior support, (2) a review of existing research syntheses focusing on behavioral interventions, (3) a new literature review of current pertinent research, and (4) an evaluative discussion of the synthesis results and the field's future needs to develop effective behavioral interventions for young children with autism. The authors offer recommendations for strengthening the existing research base and advancing behavioral technology to meet the needs of the defined target population.

4.3.10. Ringdahl, J.E., Kitsukawa, K., Andelman, M.S., Call, N., Winborn, L., Barretto, A., Reed, G.K. "Differential reinforcement with and without instructional fading." *J Appl Behav Anal* 2002 Fall;35(3):291-4.

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We evaluated a differential-reinforcement-based treatment package for the reduction of problem behavior during instructional situations. Differential reinforcement of alternative behavior (DRA; compliance) was implemented across two conditions. During one condition, instructions were presented approximately once every other minute. This condition was considered the terminal goal for treatment. During the second condition, the rate of instructions was gradually increased (beginning at zero and ending when instruction rate was similar to the first condition). Results indicated that DRA with instructional fading resulted in less problem behavior than DRA without instructional fading. These results are similar to previous studies regarding the utility of instructional fading.

4.3.11. Charlop-Christy, M.H., Carpenter, M., Le, L., LeBlanc, L.A., Kellet, K. "Using the picture exchange communication system (PECS) with children with autism: assessment of PECS acquisition, speech, social-communicative behavior, and problem behavior." *J Appl Behav Anal* 2002 Fall;35(3):213-31. Publication Types: Evaluation Studies.

Claremont McKenna College, USA.

The picture exchange communication system (PECS) is an augmentative communication system frequently used with children with autism (Bondy & Frost, 1994; Siegel, 2000; Yamall, 2000). Despite its common clinical use, no well-controlled empirical investigations have been conducted to test the effectiveness of PECS. Using a multiple baseline design, the present study examined the acquisition of PECS with 3 children with autism. In addition, the study examined the effects of PECS training on the emergence of speech in play and academic settings. Ancillary measures of social-communicative behaviors and problem behaviors were recorded. Results indicated that all 3 children met the learning criterion for PECS and showed concomitant increases in verbal speech. Ancillary gains were associated with increases in social-communicative behaviors and decreases in problem behaviors. The results are discussed in terms of the provision of empirical support for PECS as well as the concomitant positive side effects of its use.

4.3.12. Joseph, R.M., Tager-Flusberg, H., Lord, C. "Cognitive profiles and social-communicative functioning in children with autism spectrum disorder." *J Child Psychol Psychiatry* 2002 Sep;43(6):807-21.

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BACKGROUND: Whether there is an unusual degree of unevenness in the cognitive abilities of children with autism spectrum disorder (ASD) and whether different cognitive profiles among children with ASD might index etiologically significant subgroups are questions of continued debate in autism research. **METHOD:** The Differential Ability Scales (DAS) and the Autism Diagnostic Observation Schedule (ADOS) were used to examine profiles of verbal and nonverbal abilities and their relationship to autistic symptomatology in

120 relatively high-functioning children with ADI-confirmed diagnoses of autism. **RESULTS:** Discrepancies between verbal and nonverbal ability scores occurred at a significantly higher rate than in the DAS normative sample (30%) in both a younger group of 73 children (56%) with a mean age of 5;5 and an older group of 47 children (62%) with a mean age of 8;11. Discrepancies were mainly in favor of nonverbal ability in the younger group, but occurred equally in favor of verbal and nonverbal abilities in the older group. Comparison of the two age groups suggested a growing dissociation between verbal and nonverbal (and particularly visual processing) skills with age. In the older group, children with discrepantly higher nonverbal abilities demonstrated significantly greater impairment in social functioning, as measured on the ADOS, independent of absolute level of verbal and overall ability. **CONCLUSIONS:** These findings demonstrate a high rate of uneven cognitive development in children with ASD. Indications of a dissociation between verbal and visual-perceptual skills among the older children, and the specific association of discrepantly high nonverbal skills with increased social symptoms suggest that the nonverbal > verbal profile may index an etiologically significant subtype of autism.

4.3.13. van Berckelaer-Onnes, I.A., van Loon, J., Peelen, A. "Challenging behaviour: a challenge to change." *Autism* 2002 Sep;6(3):259-70.

People with intellectual disability often exhibit severe behavioural problems. Treatment of these problems is frequently very difficult. In The Netherlands, parents, institutes, schools and others can request the services of an independent advisory team with a pool of professionals who have experience with individuals who exhibit challenging behaviour. In this article the methods of the team will be described using a 24-year-old man as an example. The process took almost 7 years. Finally, this man, who had been living full time in one room in total isolation from the rest of the world, fulfilled his heart's desire—visiting the UK by Hovercraft.

4.3.14. Bauminger, N. "The facilitation of social-emotional understanding and social interaction in high-functioning children with autism: intervention outcomes." *J Autism Dev Disord* 2002 Aug;32(4):283-98.

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This study evaluated the effectiveness of a 7-month cognitive behavioral intervention for the facilitation of the social-emotional understanding and social interaction of 15 high-functioning children (8 to 17 years old) with autism. Intervention focused on teaching interpersonal problem solving, affective knowledge, and social interaction. Preintervention and postintervention measures included observations of social interaction, measures of problem solving and of emotion understanding, and teacher-rated social skills. Results demonstrated progress in three areas of intervention. Children were more likely to initiate positive social interaction with peers after treatment; in particular, they improved eye

contact and their ability to share experiences with peers and to show interest in peers. In problem solving after treatment, children provided more relevant solutions and fewer nonsocial solutions to different social situations. In emotional knowledge, after treatment, children provided more examples of complex emotions, supplied more specific rather than general examples, and included an audience more often in the different emotions. Children also obtained higher teacher-rated social skills scores in assertion and cooperation after treatment. The implications of these findings are discussed in terms of the effectiveness of the current model of intervention for high-functioning children with autism.

4.3.15. Toichi, M., Kamio, Y., Okada, T., Sakihama, M., Youngstrom, E.A., Findling, R.L., Yamamoto, K. "A lack of self-consciousness in autism." *Am J Psychiatry* 2002 Aug;159(8):1422-4.

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OBJECTIVE: This study investigated self-consciousness in autism. **METHOD:** An incidental memory task was conducted on 18 adults with high-functioning autism and 18 normal comparison subjects. Three kinds of orienting questions (phonological, semantic, and self-referent, i.e., "Does the word describe you?") were asked about target words (adjectives for personality traits) in order to induce different types of processing. This was followed by an unexpected recognition test. **RESULTS:** While semantic processing resulted in better memory than phonological processing in both groups, self-referent processing yielded better memory performance than semantic processing in the comparison group but not in the autistic group. **CONCLUSIONS:** The results suggest deficits in self-consciousness in individuals with autism.

4.3.16. Hoch, H., McComas, J.J., Thompson, A.I., Paone, D. "Concurrent reinforcement schedules: behavior change and maintenance without extinction." *J Appl Behav Anal* 2002 Summer;35(2):155-69.

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We evaluated the effects of concurrent schedules of reinforcement on negatively reinforced problem behavior and task completion with 3 children with autism. Results indicated that problem behavior occurred at high levels and relatively few tasks were completed when problem behavior produced a break (from tasks) and task completion produced either no consequence or a break. By contrast, problem behavior was eliminated and tasks were completed when problem behavior produced a break and task completion produced a break with access to preferred activities. Treatment gains were maintained without the use of extinction when the response requirement was increased and the schedule of reinforcement was thinned.

4.3.17. Higbee, T.S., Carr, J.E., Patel, M.R. "The effects of interpolated reinforcement on resistance to extinction in children diagnosed with autism: a preliminary investigation." *Res Dev Disabil* 2002 Jan-Feb;23(1):61-78.

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Studies on the "interpolation of reinforcement" effect (IRE) suggest that switching from an intermittent (INT) to a continuous (CRF) reinforcement schedule may result in less resistance to extinction than if extinction had followed INT alone. The finding has been examined with both human and animal participants using both free- and restricted-operant research preparations with equivocal results. In the present study, the IRE was examined in four young children diagnosed with autism using a free-operant preparation. Participants were matched into pairs and were exposed, in a counterbalanced order, to extinction following CRF "interpolated" between INT and extinction, and to extinction following INT alone. Resistance to extinction was examined by comparing the number of responses emitted during extinction and the number of sessions required to reach an extinction criterion. Responding may be less resistant to extinction following interpolated CRF reinforcement than following INT alone. Methodological refinements necessary for more conclusively demonstrating the IRE are discussed.

4.3.18. Siller, M., Sigman, M. "The behaviors of parents of children with autism predict the subsequent development of their children's communication." *J Autism Dev Disord* 2002 Apr;32(2):77-89.

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The present study focused on behaviors that caregivers of children with autism show during play interactions, particularly the extent to which the caregiver's behavior is synchronized with the child's focus of attention and ongoing activity. The study had two major findings. First, caregivers of children with autism synchronized their behaviors to their children's attention and activities as much as did caregivers of children with developmental delay and caregivers of typically developing children, matched on language capacities. Second, caregivers of children with autism who showed higher levels of synchronization during initial play interactions had children who developed superior joint attention and language over a period of 1, 10, and 16 years than did children of caregivers who showed lower levels of synchronization initially. These findings suggest a developmental link between parental sensitivity and the child's subsequent development of communication skills in children with autism. Implications for parent training interventions are discussed.

4.3.19. Fisch, G.S., Simensen, R.J., Schroer, R.J. "Longitudinal changes in cognitive and adaptive behavior scores in children and adolescents with the fragile X mutation or autism." *J Autism Dev Disord* 2002 Apr;32(2):107-14. *Comment in:*

J Autism Dev Disord. 2001 Apr;31(2):249-50.

General Clinical Research Center, School of Medicine, Yale University, New Haven, Connecticut 06520-8010, USA.

Studies of the relationship between the fragile X (FRAXA) mutation and autism have been controversial. Although there are differences between the two populations, individuals with FRAXA and autism exhibit remarkably similar aberrant behavior patterns. We examined comparably aged children and adolescents with FRAXA or autism to determine whether longitudinal changes in cognitive ability and adaptive behavior were similar in the two groups. We found decreases in IQ scores in young children with FRAXA as well as in those with autism. Declines in IQ scores were steeper among children with FRAXA. Older children and adolescents with autism exhibit stable test-retest scores, whereas older children with FRAXA continue to show decreases. Comparable declines in adaptive behavior composite scores were observed in both groups, at all ages tested, and across all adaptive behavior domains.

4.3.20. Burack, J.A., Iarocci, G., Bowler, D., Mottron, L. **"Benefits and pitfalls in the merging of disciplines: the example of developmental psychopathology and the study of persons with autism."** *Dev Psychopathol* 2002 Spring;14(2):225-37.

Department of Educational Psychology, McGill University, Montreal, Quebec, Canada.

Recent advances in the discipline of developmental psychopathology highlight the contributions of developmental thought to the study of persons with autism. This article briefly outlines primary developmental innovations in theory, methodology, and the interpretation of findings. Specifically, we discuss two sets of issues that arise from the general notion of developmental level. One set is relevant to the choice of persons that comprise the comparison group and the other to the various implications of the subjects' levels of functioning. In sum, we contend that researchers need to frame their empirical work within the context of developmental theory and methodology and interpret their findings accordingly. This will lead to scientifically compelling work and an increasingly heuristic approach to the study of persons with autism.

4.3.21. Peele, P.B., Lave, J.R., Kelleher, K.J. **"Exclusions and limitations in children's behavioral health care coverage."** *Psychiatr Serv* 2002 May;53(5):591-4.

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OBJECTIVE: The objective of this study was to identify benefit limits, diagnostic exclusions, and service exclusions of private behavioral health care plans that can influence the delivery of care to children. **METHODS:** A total of 128 commercial, employment-based behavioral health plans were examined for types of benefit limits, service exclusions, and diagnostic exclusions applicable to children. **RESULTS:** Almost half of the plans had restrictions on the number of outpatient visits, with limits ranging from 12 to 60 clinic visits a year. More than half of the plans had limitations on the number of inpatient days, ranging from 20 to 60 days a year. Diagnoses excluded from coverage included autism, mental retardation,

problems related to child abuse, and impulse control disorders, such as kleptomania and pyromania. Half of the services excluded could be categorized as either social and human services or complementary medicine rather than as mental health care. **CONCLUSIONS:** Plans commonly had service and diagnostic exclusions that could disrupt children's health care. The results of the study emphasize a need to address the types of treatment covered by mental health insurance.

4.3.22. Hastings, R.P., Brown, T. **"Behavior problems of children with autism, parental self-efficacy, and mental health."** *Am J Ment Retard* 2002 May;107(3):222-32.

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Self-efficacy has been identified in the general parenting literature as an important variable affecting parent outcomes. In the present study, 26 mothers and 20 fathers of children with autism reported on their self-efficacy, anxiety, and depression. Teachers rated the behavior problems of the children. Regression analyses showed that self-efficacy mediated the effect of child behavior problems on mothers' anxiety and depression, but there was no evidence that it functioned as a mediator for fathers. However, there was evidence that self-efficacy moderated the effect of child behavior problems on fathers' anxiety. No evidence for the moderating effect of self-efficacy was apparent for mothers. Methodological issues and the theoretical and practical implications of these results are discussed.

4.3.23. Johnson, E., Hastings, R.P. **"Facilitating factors and barriers to the implementation of intensive home-based behavioural intervention for young children with autism."** *Child Care Health Dev* 2002 Mar;28(2):123-9.

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BACKGROUND: Although international interest in intensive home-based early behavioural intervention for children with autism is increasing, there is little or no published research on the experiences of families conducting these programmes. **METHODS:** One hundred and forty-one UK parents conducting Lovaas-style interventions with their young child with autism were asked to identify factors that acted as facilitative factors and barriers to the implementation of these programmes. Parents responded to written questions contained within a questionnaire survey, and their responses were subjected to a content analysis procedure. **RESULTS:** Several of the facilitative factors and barriers were found to be similar. For example, a supportive therapy team was the most frequently cited facilitative factor, and problems recruiting and maintaining a suitable team was the most frequently reported barrier. Other factors seemed to be more independent constructs. For example, an important barrier was the lack of time and personal energy, but plenty of time

and energy was not cited as a facilitative factor. **CONCLUSIONS:** The practical implications of these results for families and for services supporting families engaged in intensive early behavioural intervention are discussed. In addition, more general implications for the designers of behavioural intervention programmes are identified.

4.3.24. Hatton, D.D., Hooper, S.R., Bailey, D.B., Skinner, M.I., Sullivan, K.M., Wheeler, A. "Problem behavior in boys with fragile X syndrome." *Am J Med Genet* 2002 Mar 1;108(2):105-16. Publication Types: Review, Review of Reported Cases.

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This study examines problem behavior over time in 59 boys with fragile X syndrome (FXS), aged 4-12 years, using the Child Behavior Checklist (CBCL). Approximately 49% of the boys scored within the borderline or clinical range on total problem behavior, while 56-57% scored in the borderline or clinical range on the attention and thought problems subscales, and 26% scored in this range on the social problems subscale. With a mean of 2.5 assessments per child, behavior problems were stable during the 3-year period of study. Total problem behavior was higher for children who displayed autistic behavior, were rated as low in adaptability, had mothers with higher maternal education levels, and were on medication. Mothers with more education also rated their children as having more attention, thought, and total problems. Children taking medication differed from boys who were not taking medication on social problems, but not on attention and thought problems. Low adaptability and more autistic characteristics predicted thought problems. Copyright 2002 Wiley-Liss, Inc.

4.3.25. Iqbal, Z. "Ethical issues involved in the implementation of a differential reinforcement of inappropriate behaviour programme for the treatment of social isolation and ritualistic behaviour in an individual with intellectual disabilities." *J Intellect Disabil Res* 2002 Jan;46(Pt 1):82-93.

School of Psychology, University of Birmingham, Birmingham, UK.

The present case study describes an adult male with a 28-year history of institutional care underpinned by a moderate intellectual disability (ID), and ritualistic behaviour congruent with features of autism or obsessive-compulsive disorder. The subject's ID was recognized early in life and he was provided with a special educational placement at 6 years of age, although his increasingly disturbed behaviour had resulted in several psychiatric admissions by early adolescence, and by the age of 20, his presentation necessitated long-term secure psychiatric care. The present report describes the application and ethical issues pertaining to a differential reinforcement of inappropriate behaviour (DRI) programme for the reduction of ritualistic behaviour and social isolation, the latter being a direct consequence of the former, one year after the subject

was admitted to a medium-secure assessment and treatment residential facility. The results suggest that, although the treatment was successful in targeting ritualization and reducing social isolation, ethical concerns extended to care staff concerns about the reinforcer adopted for the programme and the lack of informed consent from the subject. The former resulted in inconsistent application of the programme and its eventual termination. A follow-up assessment of the subject's extent of social isolation and ritualistic behaviour suggested a return to a pre-DRI level of morbidity. Limitations and suggestions for the future treatment of such cases are outlined.

4.3.26. Gardner, M.R. "Understanding and caring for the child with Asperger syndrome." *J Sch Nurs* 2001 Aug;17(4):178-84.

School of Nursing, University of Medicine and Dentistry of New Jersey, Stratford, NJ, USA.

Nurses in a variety of settings encounter children with the unfamiliar diagnosis of Asperger syndrome (AS). This disorder, which falls clinically along the autism spectrum, is receiving increasing attention because of its inclusion in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as one of the pervasive developmental disorders. The characteristic features of AS include deficits in social skills, atypical understanding of and use of pragmatic language, behavior problems, and a restricted set of interests. Cognitive abilities vary, and some children with AS have high intelligence. In addition, many children with AS have other conditions, such as attention deficit hyperactivity disorder, Tourette's syndrome, obsessive-compulsive disorder, and depression. The disorder can result in significant functional difficulties in the home, school, and community contexts. A case study highlights the features of AS, and a related individualized school health care plan demonstrates the school nurse's role in family and staff education, monitoring for comorbidities, behavioral management, medication management, support to family members, and referral.

4.3.27. Carpenter, M., Pennington, B.F., Rogers, S.J. "Understanding of others' intentions in children with autism." *J Autism Dev Disord* 2001 Dec;31(6):589-99.

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Many studies have shown that children with autism have difficulty understanding the thoughts and beliefs of other people. However, little research has been conducted on what these children understand about simpler mental states such as intentions. The current study tested the understanding of others' intentions in 2 1/2- to 5-year-old children with autism and a control group of children with other developmental delays. We used Meltzoff's (1995) test of understanding of others' unfulfilled intentions in an imitation context, with an additional "End State" condition. We found no significant between-group differences on any measure involving the understanding of others' intentions. Although within-group patterns suggested that children with autism may have a

slightly less complex understanding of others' intentions than do other children, it was clear that any deficits these children showed in this area were not as marked as those they typically show on traditional theory of mind tasks.

4.3.28. Escalona, A., Field, T., Singer - Strunck, R., Cullen, C., Hartshorn, K. "Brief report: improvements in the behavior of children with autism following massage therapy." *J Autism Dev Disord* 2001 Oct; 31(5): 513-6.

Touch Research institute, University of Miami School of Medicine, FL 33101, USA.

Twenty children with autism, ages 3 to 6 years, were randomly assigned to massage therapy and reading attention control groups. Parents in the massage therapy and reading attention control groups. Parents in the massage therapy group were trained by a massage therapist to a massage their children for 15 minutes prior to bedtime every night for 1 month and the parents of the attention control group read Dr. Seuss stories to their children on the same time schedule. Conners Teacher and Parent scales, classroom and playground observations, and sleep diaries were used to assess the effects of therapy on various behaviors, including hyperactivity, stereotypical and off-task behavior, and sleep problems. Results suggested that the children in the massage group exhibited less stereotypic behavior and showed more on task and social relatedness behavior during play observations at school, and they experienced fewer sleep problems at home.

4.3.29. Salt, J., Sellars, V., Shemilt, J., Boyd, S., Coulson, T., McCool, S. "The Scottish Centre for Autism preschool treatment programme. I: A developmental approach to early intervention." *Autism* 2001 Dec; 5(4): 362-73.

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Early intervention is an area of intense current interest for parents and professionals. This article describes a mainstream National Health Service (NHS) approach to early intervention, developed at the Scottish Centre for Autism. The aims of treatment are to improve the child's early social communication and social interaction skills, leading to the potential development of play and flexibility of behaviour. This is achieved by 1:1 intensive treatment by trained therapists, and a schedule of parent training. The treatment protocol incorporates a child led approach; the use of imitation as a therapeutic strategy; using language contingent on activities; and the introduction of flexibility into play and social exchanges.

4.3.30. Stone, W.L., Yoder, P.J. "Predicting spoken language level in children with autism spectrum disorders." *Autism* 2001 Dec; 5(4):341-61.

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Thirty five children who received an autism spectrum diagnosis at the age of 2 years (24 with autism, 11 with PDD-NOS) were re-evaluated 2 years later to examine factors related to the development of spoken language. Child variables (play level, motor imitation ability and joint attention) and environmental variables (socioeconomic status and hours of speech/language therapy between ages 2 and 3) were used to predict an aggregate measure of language outcome at age 4. After controlling for age 2 language skills, the only significant predictors were motor imitation and number of hours of speech/language therapy. Implications of these results for understanding the early developmental course of autism spectrum disorders and the effects of intervention are discussed.

4.3.31. Bishop, D.V., Baird, G. "Parents and teacher report of pragmatic aspects of communication: use of the children's communication checklist in a clinical setting." *Dev Med Child Neurol* 2001 Dec; 43 (12) :809-18.

Department of Experimental Psychology, University of Oxford, U.K.

The Children's Communication Checklist (CCC) was developed as an objective assessment of pragmatic aspects of children's communication difficulties. We aimed to (1) see whether the checklist provided valid and reliable information when completed by parents, and (2) consider its usefulness in a clinical context. Checklists were completed by parents and a professional who knew the child well for all 5 to 17-year-old referrals to a tertiary development paediatrics centre over a 31-month period. Children who were not yet speaking in sentences were excluded. From a sample of 151 children (81% male; mean age 8.7 years) with pervasive or specific development disorders, valid checklists were completed by 119 parents and 93 professionals. Reliability as measured by internal consistency was 0.7 or higher for most scales. Correlations between ratings for parents and professionals were in the range of 0.30 to 0.58 for individual pragmatic scales, with a correlation of 0.46 (n=82) for the pragmatic composite. For both parents and professionals, the pragmatic composite was lowest for children with a diagnosis of autism; intermediate for those with a diagnosis of Asperger syndrome, pervasive developmental disorder not otherwise specified or attention-deficit-hyperactivity disorder (ADHD); and highest for those with a diagnosis of specific learning disability. The strongest relation between the pragmatic composite and diagnosis was seen when ratings from parents and professionals were combined. Differences between diagnostic groups were not explicable in terms of age or verbal IQ.

4.3.32. Shriberg, L.D., Paul, R., McSweeney, J.L., Klin, A.M., Cohen, D.J., Volkmar, F.R. "Speech and prosody characteristics of adolescents and adults with high-functioning autism and Asperger syndrome." *J Speech Lang Hear Res* 2001 Oct; 44(5):1097-115.

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Speech and prosody-voice profiles for 15 male speakers with High-Functioning Autism (HFA) and 15 male speakers with Asperger syndrome (AS) were compared to one another and to profiles for 53 typically developing male speakers in the same 10 - to 50-years age range. Compared to the typically developing speakers, significantly more participants in the both the HFA and AS groups had residual articulation distortion errors, uncodable utterances due to discourse constraints, and utterances coded as inappropriate in the domains of phrasing, stress, and resonance. Speakers with AS were few statistically significant differences between the two groups of speakers with pervasive developmental disorders. Discussion focuses on perceptual-motor and social sources of differences in the prosody-voice findings for findings for typical speakers, including comment on the grammatical, pragmatic, and affective aspects of prosody.

4.3.33. Mueller, M.M., Wilczynski, S.M., Moore, J.W., Fusilier, I., Trahan, D. "Antecedent manipulations in a tangible condition: effects of stimulus preference on aggression." *J Appl Behav Anal* 2001 Summer;34(2):237-40.

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After a functional analysis indicated that aggression of an 8-year-old boy with autism was maintained by access to preferred items, antecedent manipulations involving the relative preference of restricted and noncontingently available stimuli were conducted. Restricting highly preferred items evoked the highest rates of aggression regardless of the preference level of the noncontingently available alternative items. Restricting less preferred stimuli was associated with moderate rates of aggression even when the alternative items were more preferred.

4.3.34. Hagopian, L.P., Wilson, D.M., Wilder, D.A. "Assessment and treatment of problem behavior maintained by escape from attention and access to tangible items." *J Appl Behav Anal* 2001 Summer;34(2):229-32.

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The results obtained from two consecutive functional analyses conducted with a 6-year-old child with autism are described. In the initial functional analysis, the highest rates of problem behavior occurred in the play condition. In that condition, the delivery of attention appeared to occasion problem behaviors. A second functional analysis was conducted wherein an escape from attention condition and a tangible condition were added. In the second functional analysis, higher rates of responding were observed in the escape from attention and tangible conditions. The results suggested that problem behavior was maintained by negative reinforcement in the form of escape from attention and positive reinforcement in the form of gaining access to preferred tangible items. Problem behavior was treated using functional communication training combined with noncontingent reinforcement.

4.3.35. Mudford, O.C., Martin, N.E., Eikeseth, S., Bibby, P. "Parent-managed behavioral treatment for preschool children with autism: some characteristics of UK programs." *Res Dev Disabil* 2001 May-Jun;22(3):173-82. Publication Types: Evaluation Studies.

Keele University, England.

Early intensive behavioral intervention for autism has attracted controversy since Lovaas (1987) reported that 47% of his experimental group attained normal functioning. We summarize child and program data from 75 children receiving EIBI in the UK. The majority of children (57%) started treatment later than in Lovaas (1987), and 16% did not exceed his minimum IQ criterion. Children experienced fewer hours of treatment (mean of 32 hours vs. 40 hours per week), and their programs received relatively infrequent supervision. 21% of programs received supervision from individuals currently accredited as competent to provide Lovaas's treatment. No child started early enough, and received 40 hours per week, and had accredited supervision. Due to these variations from his model, Lovaas (1987) findings are unlikely to be replicated for this sample of children.

4.3.36. Drasgow, E., Halle, J.W., Phillips, B. "Effects of different social partners on the discriminated requesting of a young child with autism and severe language delays." *Res Dev Disabil* 2001 Mar-Apr;22(2):125-39.

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We examined the effects of two adult social partners on the requesting repertoire of a young child with autism and severe language delays. We used a multiple-schedule design (Kazdin, 1982) to evaluate the request topography that the participant emitted relative to each social partner's contingent differential reinforcement for specific requesting forms. The contingencies associated with each adult were reversed after the participant reached a preestablished criterion of discriminated responding. The participant learned to request in a discriminated manner in the presence of each social partner. Implications of these results are discussed.

4.3.37. Progar, P.R., North, S.T., Bruce, S.S., DiNovi, B.J., Nau, P.A., Eberman, E.M., Bailey, J.R., Jr., Nussbaum, C.N. "Putative behavioral history effects and aggression maintained by escape from therapists." *J Appl Behav Anal* 2001 Spring;34(1):69-72.

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Differentially higher rates of aggression in treatment sessions occurred in the presence of two staff members who had previously worked with the participant at another facility. Adding an edible reinforcer for compliance and the absence of aggression in sessions conducted by these two staff members decreased aggression to rates similar to those obtained with less familiar therapists. Results suggest that embedding positive reinforcement within a demand context

recreation conditions) were conducted for 5 students. Results suggested that stereotypy was multiply determined or occurred across all assessment conditions. For 2 students, stereotypy was associated with positive and negative reinforcement and the absence of environmental stimulation. For 2 other students, stereotypy occurred at high levels across all experimental conditions. For the 5th student, stereotypy was associated with negative reinforcement and the absence of environmental stimulation. In Study 2, the stereotypy of 1 student was further analyzed on a function-by-function basis. Within a concurrent-schedules procedure, alternative responses were taught to the student using functional communication training. The results of Study 2 showed that similar topographies of stereotypy, based on qualitatively different reinforcers, were reduced only when differential reinforcement contingencies for alternative forms of communication were implemented for specific response-reinforcer relations. Our results suggest that the causes of stereotypy for students with autism are complex and that the presumed association between response topography and behavioral function may be less important than previously realized.

4.3.44. Dawson, G., Ashman, S.B., Carver, L.J. "The role of early experience in shaping behavioral and brain development and its implications for social policy." *Dev Psychopathol* 2000 Autumn;12(4):695-712.

Department of Psychology and Center on Human Development and Disability, University of Washington, Seattle 98195, USA.

This article provides a targeted review of the scientific literature on the effects of experience on early brain and behavioral development and later outcome as it pertains to risk for some forms of child psychopathology. It is argued that ample evidence exists indicating that the prenatal and early postnatal years likely represent a sensitive period with respect to the effects of stress on the developing nervous system and behavioral outcome, and with respect to the long-term beneficial effects of early interventions on brain and behavioral development for some genetically based disorders, such as phenylketonuria and autism. Moreover, evidence suggests that parental mental health during the first years of life has a significant influence on early brain activity and behavior, and long-term behavioral outcome. It is concluded that, although prevention and early intervention efforts should not exclusively focus on the earliest years of development, such efforts should begin during this period. By directing such efforts toward promoting optimal prenatal and infant-toddler development, the long-term negative consequences of factors that have their greatest influences during early development and which set the stage for future development can be minimized or avoided entirely. Several recommendations for public policy and future research pertaining to the effects of early experience on child outcome are offered.

4.3.45. Yarbrough, S.C., Carr, E.G. "Some relationships between informant assessment and functional analysis of problem behavior." *Am J Ment Retard* 2000 Mar;105(2):130-51.

State University of New York at Stony Brook, USA.

The strengths and limitations of informant assessment of problem behavior was investigated through examination of such behavior across seven situations and 3 participants. The results of informant assessment were compared to those obtained from functional analysis to determine some of the parameters under which informant assessment might provide a practical alternative to functional analysis. The results showed that informant hypotheses about the function of problem behavior were validated by subsequent functional analyses only when informants identified their hypotheses as involving situations likely to evoke problem behavior. Hypotheses involving situations that informants rated as less likely to evoke problem behavior were not validated by subsequent functional analyses. The implications of these findings for improving the validity of informant assessment are discussed.

4.3.46. Britton, L.N., Carr, J.E., Kellum, K.K., Dozier, C.L., Weil, T.M. "A variation of noncontingent reinforcement in the treatment of aberrant behavior." *Res Dev Disabil* 2000 Nov-Dec;21(6):425-35.

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We examined the effectiveness of a variation of noncontingent reinforcement (NCR) that incorporated a stimulus-delay procedure in the reduction of aberrant behavior maintained by positive reinforcement. Functional analyses for three individuals diagnosed with developmental disabilities indicated that their behaviors were maintained by positive reinforcement: one in the form of access to a tangible item, another by attention, and the third by physical contact. We implemented NCR with the delay procedure with two participants using reversal designs to evaluate effects. We also compared this NCR variation and DRO with the third participant to evaluate reinforcer-delivery rates. The variation of NCR was successful in reducing all aberrant behavior to near-zero levels. A comparison of reinforcer delivery between NCR with the stimulus-delay procedure and DRO demonstrated that the participant accessed more reinforcement with NCR. Results are discussed in the context of enhancing decelerative interventions with emphases on minimizing response effort for caregivers and maximizing access to reinforcement for the individuals.

4.3.47. Saltzman, J., Strauss, E., Hunter, M., Archibald, S. "Theory of mind and executive functions in normal human aging and Parkinson's disease." *J Int Neuropsychol Soc* 2000 Nov;6(7):781-8.

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Although the majority of research in theory of mind (TOM) has focused on young children or individuals with autism, recent investigations have begun to look at TOM throughout the lifespan and in other neurological and psychiatric populations. Some have suggested that TOM may represent

a dissociable, modular brain system that is related to, but separable, from other brain functions including executive functions (EF). Recently, studies have shown that TOM performance can be compromised following an acquired brain insult (e.g., damage to the right hemisphere). However, the relationship of such impaired TOM performance to other brain functions in these cases has not been explored. This study investigated the effects of both normal human aging and Parkinson's disease on TOM. The relationship of TOM performance and EF in these groups was also examined. The results suggested that although TOM performance appeared compromised in the group of individuals with Parkinson's disease, the elderly control participants were relatively unimpaired relative to younger individuals. Significant relationships between several measures of TOM and EF were also found. The implications of these findings, and also the finding that failure on one measure of TOM did not necessarily predict failure on all measures of TOM, are discussed.

4.3.48. Rogers, S.J. "Interventions that facilitate socialization in children with autism." *J Autism Dev Disord* 2000 Oct;30(5):399-409.

University of Colorado Health Sciences Center, JFK Partners, Denver 80262, USA.

Social dysfunction is perhaps the most defining and handicapping feature of autism. Improved social functioning has long been considered one of the most important intervention outcomes. A variety of social interventions have been designed, empirically examined, and published in the autism literature. Children with autism have been found to be responsive to a wide variety of interventions aimed at increasing their social engagement with others, both adults and peers. Successful strategies employing peer-mediated approaches and peer tutoring have involved typically developing peers. Furthermore, several studies have demonstrated that social engagement directly affects other important behaviors like language, even when these behaviors are not specifically targeted by the teaching program. Thus, while an area of severe involvement, social behavior is also responsive to intervention.

4.3.49. Schreibman, L. "Intensive behavioral/psychoeducational treatments for autism: research needs and future directions." *J Autism Dev Disord* 2000 Oct;30(5):373-8.

University of California, San Diego, USA.

It is widely acknowledged that, to date, the forms of treatment enjoying the broadest empirical validation for effectiveness with individuals with autism are those treatments based upon a behavioral model and that such treatments are best implemented intensively and early in the child's development. This paper describes several features important in the success of this model and presents remaining issues to be addressed for improving treatment effectiveness. While it is appreciated that there is no "one size fits all" treatment for children with autism, there is as yet no established protocol for relating specific child, family, target behavior, and treatment variables

to individualized treatment regimens. Future research needs to include well-conceived and methodologically rigorous investigations allowing for the determination of these important variables.

4.3.50. Hanley, G.P., Iwata, B.A., Thompson, R.H., Lindberg, J.S. "A component analysis of "stereotypy as reinforcement" for alternative behavior." *J Appl Behav Anal* 2000 Fall;33(3):285-97.

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Results from several studies have suggested that the opportunity to engage in stereotypic behavior may function as reinforcement for alternative, more socially desirable behaviors. However, the procedural components of this intervention include several distinct operations whose effects have not been analyzed separately. While measuring the occurrence of stereotypy and an alternative behavior (manipulation of leisure materials), we exposed 3 participants to three or four components of a "stereotypy as reinforcement" contingency: (a) continuous access to materials, (b) prompts to manipulate materials, (c) restricted access to stereotypy (i.e., response blocking), and (d) access to stereotypy contingent on manipulating the materials. Continuous access to materials and prompting (a and b) produced negligible results. Restriction of stereotypy (c) produced a large increase in the alternative behavior of 2 participants, suggesting that response restriction per se may occasion alternative behavior. However, contingent access to stereotypy (d) was necessary to increase the 3rd participant's object manipulation; this finding provided some support for the use of stereotypy as reinforcement for alternative behavior. Finally, when transfer of the effects of intervention was assessed during periods in which active intervention components were withdrawn, the alternative behavior was maintained for 1 participant.

4.3.51. Katz, R.C., Cacciapaglia, H., Cabral, K. "Labeling bias and attitudes toward behavior modification revisited." *J Behav Ther Exp Psychiatry* 2000 Mar;31(1):67-72.

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Twenty-three years ago, Woolfolk, Woolfolk and Wilson (1977, *Journal of Consulting and Clinical Psychology*, 45, 184-191) described a study about labeling bias and attitudes toward behavior modification. When videotaped depictions of behavior modification procedures were described as "humanistic education", college students rated them more favorably than when the same procedures were called "behavior modification". One implication of this study is that behavioral terminology may be perceived as dehumanizing by potential consumers, leading to lower acceptance of the approach regardless of its effectiveness. With lower acceptance comes the risk of under utilization. More than two decades have passed since the Woolfolk et al. study was published so we felt the time was right to repeat the experiment with a new generation of students. In our study, two groups of college undergraduates (N = 144) gave their opinions about a 10 minute videotape that showed a therapist

working with an autistic child. The therapist used behavior modification procedures to treat the child, except in one case the procedures were described as "humanistic educative therapy", and in the other as "behavior modification". An appropriate rationale was provided for each of the two conditions. Unlike Woolfolk et al., we found no differences in how the two depictions were evaluated. In both cases, they were perceived favorably regardless of what they were called, as were the personal qualities of the therapist. These results suggest that negative attitudes toward behavior modification have weakened over the last two decades, and there is wider public acceptance of behavioral treatments now than there was then. Implications of the study are briefly discussed.

4.3.52. Mawhood, L., Howlin, P., Rutter, M. "Autism and developmental receptive language disorder—a comparative follow-up in early adult life. I: Cognitive and language outcomes." *J Child Psychol Psychiatry* 2000 Jul;41(5):547-59.

Department of Psychology, St George's Hospital Medical School, London, UK.

In this paper we compare adult outcome in a group of young men with autism and a group with developmental receptive language disorders. The two groups were first assessed in early childhood, when aged 7 to 8 years of age. Although matched at that time for nonverbal IQ (mean 92-93) and expressive language ability, the Autism group was significantly more impaired on most measures of social and communication skills and stereotyped behaviours. A later follow-up, in mid-childhood, suggested that although the groups were still quite distinct, social and behavioural problems had become more apparent in the Language group. The current study was completed when the participants were aged, on average, 23 to 24 years. The findings indicated that verbal IQ and receptive language scores had improved significantly more in the Autism group than in the Language group, over time. Moreover, although the Language group were less severely impaired in their social use of language, many showed a number of abnormal features in this domain. There were no differences between the groups on tests of reading or spelling. Discriminant function analysis, which had clearly distinguished between the groups as children, now showed much greater overlap between them. Regression analysis indicated that although early language ability appeared to be related to outcome in the Autism group, in the Language group there was little association between measures of childhood functioning and later progress. The implications of these findings for understanding the nature of the underlying deficit in autism and the relationship between the two disorders are discussed.

4.3.53. Beversdorf, D.Q., Smith, B.W., Crucian, G.P., Anderson, J.M., Keillor, J.M., Barrett, A.M., Hughes, J.D., Felopulos, G.J., Bauman, M.L., Nadeau, S.E., Heilman, K.M. "Increased discrimination of "false memories" in autism spectrum disorder." *Proc Natl Acad Sci U S A* 2000 Jul 18;97(15):8734-7.

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Individuals with autism spectrum disorder (ASD) have impaired ability to use context, which may manifest as alterations of relatedness within the semantic network. However, impairment in context use may be more difficult to detect in high-functioning adults with ASD. To test context use in this population, we examined the influence of context on memory by using the "false memory" test. In the false memory task, lists of words were presented to high-functioning subjects with ASD and matched controls. Each list consists of words highly related to an index word not on the list. Subjects are then given a recognition test. Positive responses to the index words represent false memories. We found that individuals with ASD are able to discriminate false memory items from true items significantly better than are control subjects. Memory in patients with ASD may be more accurate than in normal individuals under certain conditions. These results also suggest that semantic representations comprise a less distributed network in high-functioning adults with ASD. Furthermore, these results may be related to the unusually high memory capacities found in some individuals with ASD. Research directed at defining the range of tasks performed superiorly by high-functioning individuals with ASD will be important for optimal vocational rehabilitation.

4.3.54. Miller, N., Neuringer, A. "Reinforcing variability in adolescents with autism." *J Appl Behav Anal* 2000 Summer;33(2):151-65.

Psychology Department, Reed College, Portland, Oregon 97202, USA.

Five adolescents with autism, 5 adult control participants, and 4 child controls received rewards for varying their sequences of responses while playing a computer game. In preceding and following phases, rewards were provided at approximately the same rate but were independent of variability. The most important finding was that, when reinforced, variability increased significantly in all groups. Reinforced variability could provide the necessary behavioral substrate for individuals with autism to learn new responses.

4.3.55. Coplan, J. "Counseling parents regarding prognosis in autistic spectrum disorder." *Pediatrics* 2000 May;105(5):E65.

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A triaxial model for autistic spectrum disorder (ASD) is presented, incorporating age, degree of intelligence, and severity of autistic features. As the name implies, ASD can vary in degree of expression from minimal to profound. Furthermore, the symptoms of ASD change in predictable ways with the passage of time. For example, echolalia during early childhood may be replaced by verbal literalism and difficulty with verbal humor during later childhood or adolescence. The prognosis for children with ASD is governed by the joint impact of the degree of expression of ASD and the degree of developmental delay, if any. All combinations

of ASD and intellect are possible (ie, severe ASD plus severe mental retardation, severe ASD plus normal general intelligence, and so forth). The relationship among these 3 parameters-severity of ASD, level of general intelligence, and change in symptom expression over time, is represented schematically as a 3-dimensional graph. The utility of this graph as a counseling tool, and as the basis for future research on the prognosis of ASD are discussed.

4.3.56. Stone, W.L., Ousley, O.Y., Hepburn, S.L., Hogan, K.L., Brown, C.S. "Patterns of adaptive behavior in very young children with autism." *Am J Ment Retard* 1999 Mar;104(2):187-99. Publication Types: Clinical Trial.

Vanderbilt University School of Medicine, USA.

The Vineland Adaptive Behavior Scales were used to investigate patterns of adaptive behavior in children with autism who were under 36 months of age. Subjects were 30 children with autism and 30 children with developmental delay matched on CA and MA. Relative to controls, the autistic group demonstrated weaker socialization and communication skills and greater discrepancies between adaptive behavior and MA. Different patterns of relations between adaptive behavior domains and cognitive and language skills were obtained for the two groups. Preliminary support for the utility of adaptive behavior profiles in identifying subgroups of children with autism is provided. Results are discussed in terms of their implications for early diagnosis of autism.

4.3.57. Edelson, S.M., Edelson, M.G., Kerr, D.C., Grandin, T. "Behavioral and physiological effects of deep pressure on children with autism: a pilot study evaluating the efficacy of Grandin's Hug Machine." *Am J Occup Ther* 1999 Mar-Apr;53(2):145-52. Publication Types: Clinical Trial, Randomized Controlled Trial.

Autism Research Institute, San Diego, California, USA.

OBJECTIVE: One symptom common to many persons with autism is a high arousal or anxiety level. This study investigated the effects of deep pressure on arousal and anxiety reduction in autism with Grandin's Hug Machine, a device that allows self-administration of lateral body pressure. **METHOD:** Twelve children with autism were randomly assigned to either an experimental group (receiving deep pressure) or a placebo group (not receiving deep pressure but in the disengaged Hug Machine). All children received two 20-min sessions a week over a 6-week period. Arousal was measured behaviorally with the Conners Parent Rating Scale and physiologically with galvanic skin response (GSR) readings. **RESULTS:** Behavioral results indicated a significant reduction in tension and a marginally significant reduction in anxiety for children who received the deep pressure compared with the children who did not. Additionally, children in the experimental group, whose GSR measures decreased, on average, after deep pressure, were somewhat more likely to have higher GSR arousal a priori. **CONCLUSION:** These preliminary findings support the hypothesis that deep

pressure may have a calming effect for persons with autism, especially those with high levels of arousal or anxiety.

4.3.58. Mace, A.B., Shapiro, E.S., Mace, F.C. "Effects of warning stimuli for reinforcer withdrawal and task onset on self-injury." *J Appl Behav Anal* 1998 Winter;31(4):679-82.

Lehigh University, USA.

Results of a functional analysis of self-injurious behavior (SIB) in a child with autism showed that her SIB was maintained by access to preferred objects and escape or avoidance of task demands. Extinction and noncontingent reinforcement treatments were supplemented by presenting a statement combined with a picture cue at 30-s intervals indicating that a preferred object would be removed or a task would be presented. Warning stimuli in combination with extinction and noncontingent reinforcement reduced SIB to acceptable levels. SIB rates remained comparatively high in a control condition consisting of a 2-min delay to onset of reinforcer removal or task demands.

4.3.59. Quill, K.A. "Environmental supports to enhance social-communication." *Semin Speech Lang* 1998;19(4):407-22; quiz 422-3; 424. Publication Types: Review, Review, Tutorial.

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"Environmental support" is a general term used to define the systematic use of explicit visual and/or social cues to clarify meaning for children with autism. Environmental supports can serve as a compensatory means to structure and enhance language understanding, social engagement, and social-communicative interactions. The unique and atypical developmental patterns associated with autism provide the rationale for the use of two environmental supports: visually cued instruction and modified sociolinguistic input. Using empirical research, multiple examples of environmental supports to enhance social-communication are provided.

4.3.60. Simonoff, E. "Genetic counseling in autism and pervasive developmental disorders." *J Autism Dev Disord* 1998 Oct;28(5):447-56. Publication Types: Review, Review, Tutorial.

Section of Child and Adolescent Psychiatry, Guy's Medical School, Guy's Hospital, London, United Kingdom.

With increasing awareness of the importance of genetic influences on autism, there is now a demand from families with an affected member for advice regarding their risk of having an autistic child. Research evidence currently available makes it possible to give families empirical recurrence risks. It is desirable that this information is imparted by those with joint expertise in the diagnosis and treatment of autism and in the genetics of complex modes of inheritance. A protocol for genetic counseling is described, along with the key elements that influence the recurrence risks given to individual couples. There is a need to give information regarding recurrence risks not only for autism but also for the broader phenotype. In addition, couples may have other issues they wish to discuss, which may influence their reproductive decisions.

MANAGEMENT

Therapeutics

4.4.1. Botting, N., Conti-Ramsden, G. "Autism, primary pragmatic difficulties, and specific language impairment: can we distinguish them using psycholinguistic markers?" *Dev Med Child Neurol.* 2003 Aug;45(8):515-24.

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Three groups of children with communication disorders were examined using a series of psycholinguistic markers to explore whether the tasks could identify children with impairments other than specific language impairment (SLI), and to examine whether the different groups within this clinical population could be distinguished reliably from one another. The groups comprised children with autistic spectrum disorders (ASD; n = 13, all males; mean age 10 years 10 months, range 10 years 2 months to 12 years 6 months); children with primary pragmatic language impairment (PLI) but who did not have definite ASD diagnoses (n = 25, 22 males, three females; mean age 11 years 3 months, range 10 years 2 months to 12 years 5 months); and children with specific language impairment (SLI) without marked pragmatic language difficulties (n = 29, 25 males, 4 females; mean age 10 years 10 months, range 10 years 2 months to 11 years 9 months). Clinical markers examined were: the Children's Non-Word Repetition (CNRep), the Past Tense Task (PTT), and the Clinical Evaluation of Language Fundamentals, Recalling Sentences. First, it was found that the a priori groupings were not sufficiently defined and that four groups were actually present. The PLI group was in fact two separate samples: those with PLI pure and those with some autistic-like behaviours (referred to here as PLI plus, following Bishop 1998). Second, group comparisons indicated that CNRep was significantly lower for children with SLI than all other groups (although this measure was not such a good discriminator using a specificity analysis). Third, the markers were able to discriminate between all types of communication impairment in normal control participants (n = 100; 51 females, 49 males; mean age 11 years, range 10 years 5 months to 11 years 6 months) with sensitivity levels of at least 75% and specificity of 80%. Recalling Sentences was the most efficient marker for all groups. Finally, analysis showed that children with PLI plus could be accurately distinguished from all others, scoring most favourably overall on communication markers and on performance IQ scores.

4.4.2. Wilson, S., Djukic, A., Shinnar, S., Dharmani, C., Rapin, I. "Clinical characteristics of language regression in children." *Dev Med Child Neurol.* 2003 Aug;45(8):508-14.

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The spectrum of language regression in childhood is incompletely understood. To describe the features of this disorder more fully, we reviewed the records of 196 consecutive children (143 males and 53 females) with language regression or perceived plateau evaluated between 1988 and 1994 by a child neurologist. Mean age at regression was 21.2 months and the mean interval to referral was 34.8 months. A trigger for the regression was identified in 74 of the children

(38%) and was associated with a more rapid regression. Mean age at follow-up was 64 months (SD 55). Seventy per cent of the children became nonverbal, and 75% were cognitively impaired. Language regression was associated with a more global autistic regression in 93% of children. There was a history of seizures in 15% of the children. Some recovery occurred in 61% but only one child recovered fully. Improvement was more likely in the 49% who were entirely developmentally normal before the regression. We conclude that language regression in childhood is a serious disorder with significant long-term morbidity.

4.4.3. Charman, T., Drew, A., Baird, C., Baird, G. "Measuring early language development in preschool children with autism spectrum disorder using the MacArthur Communicative Development Inventory (Infant Form)." *J Child Lang.* 2003 Feb;30(1):213-36.

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Parent report data on early language development measured using the MacArthur Communicative Development Inventory (CDI-Infant Form) was collected on 134 preschool children with autism spectrum disorder. The pattern of development of understanding of phrases, word comprehension and expression, and production of gestures, was compared to the typical pattern. In common with typical development there was considerable variability in language acquisition, although for the group as a whole this was significantly delayed compared to the normal course. In addition, atypical patterns were identified in the emergence of language skills in the sample. Comprehension of words was delayed in comparison to word production, and production of early gestures (involving sharing reference) was delayed relative to production of later gestures (involving use of objects). However, other aspects of language development were similar to that found in typically developing infants, including word comprehension being in advance of word production in absolute terms, gesture production acting as a 'bridge' between word comprehension and word production and the broad pattern of acquisition across word categories and word forms. The implications for assessment and intervention with preschool children with autism spectrum disorder are discussed.

4.4.4. Desha, L., Ziviani, J., Rodger, S. "Play preferences and behavior of preschool children with autistic spectrum disorder in the clinical environment." *Phys Occup Ther Pediatr.* 2003;23(1):21-42.

Department of Occupational Therapy, University of Queensland, Brisbane, QLD 4072, Australia.

The play of children with autistic spectrum disorder (ASD) is a valuable medium for assessment and intervention, and its analysis has the potential to aid diagnosis. This study investigated spontaneous play behavior and play object preferences for 24 preschool children with ASD in a typical occupational therapy clinical environment. Play behavior was rated and choice of play object noted at 10-second intervals

from a 15-minute video recording of unstructured play. Statistical analyses indicated that play behavior was consistent with descriptions in the literature. In addition, the children demonstrated clear preferences for play objects in the form of popular characters (e.g., Thomas the Tank Engine) and those with sensorimotor properties. We propose that the inclusion of preferred play objects in a clinical environment may increase intrinsic motivation to play, and thereby enhance assessment and intervention.

4.4.5. Ceponiene, R., Lepisto, T., Shestakova, A., Vanhala, R., Alku, P., Naatanen, R., Yaguchi, K. "Speech-sound-selective auditory impairment in children with autism: they can perceive but do not attend." *Proc Natl Acad Sci U S A*. 2003 Apr 29;100(9):5567-72. Epub 2003 Apr 17.

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In autism, severe abnormalities in social behavior coexist with aberrant attention and deficient language. In the attentional domain, attention to people and socially relevant stimuli is impaired the most. Because socially meaningful stimulus events are physically complex, a deficiency in sensory processing of complex stimuli has been suggested to contribute to aberrant attention and language in autism. This study used event-related brain potentials (ERP) to examine the sensory and early attentional processing of sounds of different complexity in high-functioning children with autism. Acoustically matched simple tones, complex tones, and vowels were presented in separate oddball sequences, in which a repetitive "standard" sound was occasionally replaced by an infrequent "deviant" sound differing from the standard in frequency (by 10%). In addition to sensory responses, deviant sounds elicited an ERP index of automatic sound-change discrimination, the mismatch negativity, and an ERP index of attentional orienting, the P3a. The sensory sound processing was intact in the high-functioning children with autism and was not affected by sound complexity or "speechness." In contrast, their involuntary orienting was affected by stimulus nature. It was normal to both simple- and complex-tone changes but was entirely abolished by vowel changes. These results demonstrate that, first, auditory orienting deficits in autism cannot be explained by sensory deficits and, second, that orienting deficit in autism might be speech-sound specific.

4.4.6. Coldren, J.T., Halloran, C. "Spatial reversal as a measure of executive functioning in children with autism." *J Genet Psychol*. 2003 Mar;164(1):29-41.

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The purpose of this experiment was to compare the executive functioning performance of children with autism with chronological- and verbal-matched controls in a spatial-reversal task. Three groups of children participated in this experiment. One group was identified as having autism (7 boys), the 2nd group contained 7 typically developing children

(6 boys, 1 girl) who were matched to the 1st group based on their verbal performance, and the 3rd group contained 7 typically functioning children (6 boys, 1 girl) matched to the 1st group based on chronological age. Each group was given a spatial-reversal task containing 2 problems. In the 1st problem, children selected a toy on a particular side in a pair. In the 2nd problem, the contingencies were reversed such that children were to choose the toy on the opposite side. Children with autism generally performed worse than comparison groups as indicated by their overall higher rate of errors. However, these results must be qualified by considering the performance for each problem: Errors for the children with autism were infrequent during the 1st problem but increased in the 2nd, whereas errors for comparison children showed the opposite pattern. When these results from the spatial-reversal task were interpreted from the perspective of hypothesis-testing theory, the executive functioning deficiency of children with autism was found to involve the selection and testing of stereotypic response sets that were not likely to be revised or changed flexibly according to feedback from the environment or the demands of the task.

4.4.7. Rapin, I., Dunn, M. "Update on the language disorders of individuals on the autistic spectrum." *Brain Dev*. 2003 Apr;25(3):166-72. Publication Types: Review, Review, Tutorial.

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Inadequate language is a defining feature of the autism spectrum disorders (autism). Autism is a behaviorally and dimensionally defined developmental disorder of the immature brain that has a broad range of severity and many etiologies, with multiple genes involved. Early studies, which focused on the language of verbal children on the autistic spectrum, emphasized aberrant features of their speech such as unusual word choices, pronoun reversal, echolalia, incoherent discourse, unresponsiveness to questions, aberrant prosody, and lack of drive to communicate. Persistent lack of speech of some individuals was attributed to the severity of their autism and attendant mental retardation rather than possible inability to decode auditory language. Clinical study of unselected children with autism indicated that the language deficits of preschoolers fall into two broad types, perhaps with subtypes, those that involve reception and production of phonology (sounds of speech) and syntax (grammar), and those that do not but involve semantics (meaning) and pragmatics (communicative use of language, processing, and production of discourse). Except for the preschoolers' universally deficient pragmatics and comprehension of speech, many of their language deficits parallel those of non-autistic preschoolers with developmental language disorders. There is now biological support for the clinical observation that young autistic children are language disordered as well as autistic. Recent electrophysiological studies disclose auditory input abnormalities in lateral temporal cortex even in verbal individuals on the autistic spectrum. Severe receptive deficits for phonology enhance the risk for epilepsy. Genetic studies indicate that linkage to chromosome 7q31-33 is limited

to families with evidence for phonologic impairment as well as autism. Clearly, social and cognitive disorders alone provide an inadequate explanation for the range of language deficits in autism.

4.4.8. Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E., Bonnel, A.M. "Enhanced pitch sensitivity in individuals with autism: a signal detection analysis." *J Cogn Neurosci*. 2003 Feb 15;15(2):226-35. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Past research has shown a superiority of participants with high-functioning autism over comparison groups in memorizing picture-pitch associations and in detecting pitch changes in melodies. A subset of individuals with autism, known as "musical savants," is also known to possess absolute pitch. This superiority might be due to an abnormally high sensitivity to fine-grained pitch differences in sounds. To test this hypothesis, psychoacoustic tasks were devised so as to use a signal detection methodology. Participants were all musically untrained and were divided into a group of 12 high-functioning individuals with autism and a group of 12 normally developing individuals. Their task was to judge the pitch of pure tones in a "same-different" discrimination task and in a "high-low" categorization task. In both tasks, the obtained psychometric functions revealed higher pitch sensitivity for subjects with autism, with a more pronounced advantage over control participants in the categorization task. These findings confirm that pitch processing is enhanced in "high-functioning" autism. Superior performance in pitch discrimination and categorization extends previous findings of enhanced visual performance to the auditory domain. Thus, and as predicted by the enhanced perceptual functioning model for peaks of ability in autism (Mottron & Burack, 2001), autistic individuals outperform typically developing population in a variety of low-level perceptual tasks.

4.4.9. Bertone, A., Mottron, L., Jelenic, P., Faubert, J. "Motion perception in autism: a "complex" issue." *J Cogn Neurosci*. 2003 Feb 15;15(2):218-25. Publication Types: Clinical Trial, Controlled Clinical Trial.

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We present the first assessment of motion sensitivity for persons with autism and normal intelligence using motion patterns that require neural processing mechanisms of varying complexity. Compared to matched controls, our results demonstrate that the motion sensitivity of observers with autism is similar to that of nonautistic observers for different types of first-order (luminance-defined) motion stimuli, but significantly decreased for the same types of second-order (texture-defined) stimuli. The latter class of motion stimuli has been demonstrated to require additional neural computation to be processed adequately. This finding may reflect less efficient integrative functioning of the neural mechanisms that mediate visuoperceptual processing in

autism. The contribution of this finding with regards to abnormal perceptual integration in autism, its effect on cognitive operations, and possible behavioral implications are discussed.

4.4.10. Camaioni, L., Perucchini, P., Muratori, F., Parrini, B., Cesari, A. "The communicative use of pointing in autism: developmental profile and factors related to change." *Eur Psychiatry*. 2003 Feb;18(1):6-12.

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PURPOSE: To describe different longitudinal profiles in communicative abilities and symptoms severity in early autism. **METHODS:** Five children with autism, aged from 3;3 to 4;10 years at baseline, were tested for production and comprehension of imperative and declarative pointing at about 4-month intervals. Concurrently with these sessions, children were evaluated in terms of cognitive and communicative abilities, and symptoms severity. **RESULTS:** Four subjects showed a mild to severe retardation in communicative and linguistic abilities. For production, all children exhibited the imperative pointing and only one the declarative pointing. For comprehension, two subjects showed the same profile as in production ('only imperative' and 'first imperative-later declarative', respectively). One child did not show any clear comprehension of the pointing gestures produced by the experimenter, and one child was able to understand both pointing in the same session. Childhood autism rating scale (CARS) global scores tended to decrease across sessions for all subjects and different individual profiles were identified. **DISCUSSION:** Declarative or experience-sharing pointing emerged later in one child only; it remained absent in four children as production, and in two children as comprehension. A preliminary conclusion based on CARS rating, is that autism involves a symptomatology that may decrease across time even if children differ in the decreasing profile relative to specific scores.

4.4.11. Ross, D.E., Greer, R.D. "Generalized imitation and the mand: inducing first instances of speech in young children with autism." *Res Dev Disabil*. 2003 Jan-Feb;24(1):58-74. Publication Types: Clinical Trial.

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It has been suggested that the use of a generalized motor imitation sequence before a vocal model may be an effective procedure for teaching nonvocal children with autism to speak. However, the tactic has rarely been empirically demonstrated. The purpose of this experiment was to test the effects of presenting a rapid generalized motor imitation sequence before an opportunity to imitate on the vocal speech of nonvocal children with autism. Participants emitted no vocal imitations during a mand training baseline. During the intervention, a rapid motor imitation sequence was presented before an opportunity to imitate a model's vocalizations. The teacher's presentation of the rapid motor imitation sequence

was then faded by presenting an opportunity to vocally imitate without the sequence followed by an opportunity to independently mand. Results of the intervention phase indicated that all of the participants began to vocalize with the generalized motor imitation sequence and that mands were maintained during a follow-up phase and 3-month follow-up probes.

4.4.12. Krasny, L., Williams, B.J., Provencal, S., Ozonoff, S. **"Social skills interventions for the autism spectrum: essential ingredients and a model curriculum."** *Child Adolesc Psychiatr Clin N Am.* 2003 Jan;12(1):107-22.

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This article outlines the ingredients the authors feel are critical to making social skills interventions successful for children with autism spectrum disorders. The authors described basic principles for teaching social skills that capitalize on the strengths of such children, while specifically addressing their deficits. The authors applied these widely used principles to group social skills intervention. In particular, social skills groups for children with ASD need to break down complex social behaviors into concrete steps and rules that can be memorized and practiced in a variety of settings. Abstract concepts must be made concrete through a variety of visual, tangible, "hands-on" activities that make socialization fun. Visual structure and predictable routines are essential. Also critical to the success of social skills intervention are instruction and activities that provide necessary support for the language abilities of the participants. A variety of learning opportunities must be used to teach the goals and skills most relevant to children with ASD. These skills must be integrated as intervention progresses. Furthermore, interactions that require the children to focus on peers create a positive social group culture. Within this culture and environment, self-awareness and positive self-esteem can be fostered. A behavior plan that specifies individual goals for group members and a specific system for delivering rewards should be included. Other important ingredients include generalization, which is encouraged through community outings, skill practice in more naturalistic settings, and collaboration with parents and teachers to work on skills outside the group intervention. Weekly therapy does little to change basic deficits of ASD unless there is daily practice and reinforcement of the skills being learned in more natural situations. The authors hope that outlining these principles and specific techniques will encourage more clinicians to offer social skills groups and thus increase their availability around the nation and world. Continued research and treatment for social skills is necessary to provide much needed empiric evidence to determine effectiveness of such interventions.

4.4.13. Paul, R. **"Promoting social communication in high functioning individuals with autistic spectrum disorders."** *Child Adolesc Psychiatr Clin N Am.* 2003 Jan;12(1):87-106, vii. Publication Types: Review, Review, Tutorial.

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This article reviews a range of social communication interventions that have been developed for students with autism at the preschool, school age, and adolescent level. Adult-mediated and peer-mediated methods that use highly structured, child-centered, and hybrid methods are examined. Programs that provide information on generalization and maintenance are identified. A set of recommendations for programs that would seem to be most appropriate for students with Asperger syndrome is presented.

4.4.14. Souders, M.C., Freeman, K.G., DePaul, D., Levy, S.E. **"Caring for children and adolescents with autism who require challenging procedures."** *Pediatr Nurs.* 2002 Nov-Dec;28(6):555-62. Publication Types: Review, Review, Tutorial. Regional Autism Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Providing nursing care for children with autism or autistic spectrum disorders (ASD) can be challenging. As part of a larger study of 62 children with autism ages 3-8 years (Coplan et al., 2001; Levy et al., 2001) that required difficult procedures, strategies were developed for providing care that incorporated theories and knowledge from the disciplines of nursing, child development, psychology, applied behavior analysis, and pain management. Applications of these strategies are illustrated through the process of a physical exam, phlebotomy, and intravenous (IV) insertion during a health care visit. The nurse can develop a plan of care to achieve the goals of the visit and optimize the quality of the care for the child and family. Interventions presented can be individualized to each child.

4.4.15. Boser, K., Higgins, S., Fetherston, A., Preissler, M.A., Gordon, B. **"Semantic fields in low-functioning autism."** *J Autism Dev Disord.* 2002 Dec;32(6):563-82.

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Restricted semantic fields and resultant stimulus overselectivity are often thought to be typical of low-functioning autism, as is a strong visual processing preference. However, these conclusions may in part be an artifact of testing methodology. A 12-year-old, low-functioning and nonverbal autistic boy was tested on an auditory word-to-picture selection task. The picture foils were chosen to have visual features, semantic features, both, or neither in common with the correct answer. Errors were made more often to semantically than to visually related items, and he showed generalization to items that had not been explicitly trained. This is taken as evidence that his semantic fields are broader than otherwise apparent, and that he was capable of expanding his semantic representations independently of specific training.

4.4.16. Baranek, G.T. **"Efficacy of sensory and motor interventions for children with autism."** *J Autism Dev Disord.* 2002 Oct;32(5):397-422. Publication Types: Review, Review, Academic.

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Idiosyncratic responses to sensory stimuli and unusual motor patterns have been reported clinically in young children with autism. The etiology of these behavioral features is the subject of much speculation. Myriad sensory and motor based interventions have evolved for use with children with autism to address such issues; however, much controversy exists about the efficacy of such therapies. This review paper summarizes the sensory and motor difficulties often manifested in autism, and evaluates the scientific basis of various sensory and motor interventions used with this population. Implications for education and further research are described.

4.4.17. Goldstein, H. **"Communication intervention for children with autism: a review of treatment efficacy."** *J Autism Dev Disord.* 2002 Oct;32(5):373-96. Publication Types: Review, Review, Academic.

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Empirical studies evaluating speech and language intervention procedures applied to children with autism are reviewed, and the documented benefits are summarized. In particular, interventions incorporating sign language, discrete trial training, and milieu teaching procedures have been used successfully to expand the communication repertoires of children with autism. Other important developments in the field stem from interventions designed to replace challenging behaviors and to promote social and scripted interactions. The few studies of the parent and classroom training studies that included language measures also are analyzed. This article seeks to outline the extent to which previous research has helped identify a compendium of effective instructional practices that can guide clinical practice. It also seeks to highlight needs for further research to refine and extend current treatment approaches and to investigate more comprehensive treatment packages.

4.4.18. McConnell, S.R. **"Interventions to facilitate social interaction for young children with autism: review of available research and recommendations for educational intervention and future research."** *J Autism Dev Disord.* 2002 Oct;32(5):351-72. Publication Types: Review, Review, Academic.

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The purpose of this paper is to review the knowledge available from aggregated research (primarily through 2000) on the characteristics of social interactions and social relationships among young children with autism, with special attention to strategies and tactics that promote competence or improved performance in this area. In its commissioning letter for the

initial version of this paper, the Committee on Educational Interventions for Children with Autism of the National Research Council requested "a critical, scholarly review of the empirical research on interventions to facilitate the social interactions of children with autism, considering adult-child interactions (where information is available) as well as child-child interactions, and including treatment of [one specific question]: What is the empirical evidence that social irregularities of children with autism are amenable to remediation?" To do this, the paper (a) reviews the extent and quality of empirical literature on social interaction for young children with autism; (b) reviews existing descriptive and experimental research that may inform us of relations between autism and characteristics that support social development, and efforts to promote improved social outcomes (including claims for effectiveness for several specific types of intervention); (c) highlights some possible directions for future research; and (d) summarizes recommendations for educational practices that can be drawn from this research.

4.4.19. Wheless, J.W., Simos, P.G., Butler, I.J. **"Language dysfunction in epileptic conditions."** *Semin Pediatr Neurol* 2002 Sep;9(3):218-28. Publication Types: Review, Review, Tutorial.

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Epilepsy may disrupt brain functions necessary for language development by its associated intellectual disabilities or directly as a consequence of the seizure disorder. Additionally, in recent years, there has been increasing recognition of the association of epileptiform electroencephalogram (EEG) abnormalities with language disorders and autism spectrum disorders. Any process that impairs language function has long-term consequences for academic, social, and occupational adjustments in children and adolescents with epilepsy. Furthermore, impairments in specific language abilities can impact memory and learning abilities. This article reviews interictal language function in children and adults with epilepsy; epilepsy surgery and language outcome; and language disorders associated with abnormal EEGs. The relationship between epilepsy and language function is complicated as the neuroanatomic circuits common to both overlap. We demonstrate how magnetoencephalography (MEG) offers the ability to analyze the relationship of language, EEG abnormalities, and epilepsy.

4.4.20. Brownell, M.D. **"Musically adapted social stories to modify behaviors in students with autism: four case studies."** *J Music Ther* 2002 Summer;39(2):117-44.

University of Kansas, USA.

The purpose of the present study was to investigate the effect of a musical presentation of social story information on the behaviors of students with autism. Social stories are a means of incorporating an individual with autism's propensity toward visual learning with educationally necessary behavior modifications. Participants in the study were four first- and

second-grade students with a primary diagnosis of autism attending an elementary school in eastern Iowa. A unique social story was created for each student that addressed a current behavioral goal. Subsequently, original music was composed using the text of the social story as lyrics. The independent variable for this study was one of three treatment conditions: baseline (A); reading the story (B); and singing the story (C). The reading and singing versions of the social stories were alternately presented to the students using the counterbalanced treatment order ABAC/ACAB. The dependent variable was the frequency with which the target behavior occurred under each condition of the independent variable. Data were collected for a period of 1 hour following presentation of the social story. Results from all four cases indicated that both the reading condition (B) and the singing condition (C) were significantly ($p < .05$) more effective in reducing the target behavior than the no-contact control condition (A). The singing condition was significantly more effective than the reading condition only in Case Study III. For the remaining case studies, the mean frequency of the target behavior was smaller during the singing condition, but not significantly so. These results suggested that the use of a musically adapted version of social stories is an effective and viable treatment option for modifying behaviors with this population.

4.4.21. Norbury, C.F., Bishop, D.V. "Inferential processing and story recall in children with communication problems: a comparison of specific language impairment, pragmatic language impairment and high-functioning autism." *Int J Lang Commun Disord* 2002 Jul-Sep;37(3):227-51.

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An investigation is reported into the story comprehension abilities of four groups of children: those with typical specific language impairment (SLI-T), those with pragmatic language impairments who were not autistic (PLI), those with high-functioning autism (HFA) and typically developing controls. The story comprehension task required children to answer questions about the literal content of the story, as well as questions involving two types of inferences: text-connecting and gap-filling. The control children outscored the three clinical groups on story comprehension, but the group means of the clinical groups did not differ. However, categorical examination of the data revealed that children with pragmatic difficulties related to HFA were more likely to have specific inferencing deficits. Error analysis suggested that all children could make inferences, but these were not always relevant to the story context. This supports the notion of weak central coherence underlying deficits in inferencing. There were no group differences on story recall. However, there was a strong relationship between story comprehension and recall, in that those who had better comprehension tended to have better recall. It is concluded that comprehension aids recall by enabling the listener to build a more stable mental representation of the story. The pragmatic deficits seen in autism compromise this process.

4.4.22. Peretz, I. "Brain specialization for music." *Neuroscientist* 2002 Aug;8(4):372-80. Publication Types: Review, Review, Tutorial.

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Music, like language, is a universal and specific trait to humans. Similarly, music appreciation, like language comprehension, appears to be the product of a dedicated brain organization. Support for the existence of music-specific neural networks is found in various pathological conditions that isolate musical abilities from the rest of the cognitive system. Cerebrovascular accidents, traumatic brain damage, and congenital brain anomalies can lead to selective disorders of music processing. Conversely, autism and epilepsy can reveal the autonomous functioning and the selectivity, respectively, of the neural networks that subservise music. However, brain specialization for music should not be equated with the presence of a singular "musical center" in the brain. Rather, multiple interconnected neural networks are engaged, of which some may capture the essence of brain specialization for music. The encoding of pitch along musical scales is likely such an essential component. The implications of the existence of such special-purpose cortical processes are that the human brain might be hardwired for music.

4.4.23. Ruberman, L. "Psychotherapy of children with pervasive developmental disorders." *Am J Psychother* 2002;56(2):262-73. Publication Types: Review, Review of Reported Cases.

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In recent years, the role of psychotherapy in the treatment of children with pervasive developmental disorders, such as autism and Asperger's Syndrome, has been questioned. Advances in neuropsychiatry, neuropsychology, and genetics, as well as the refinement of behavioral and educational techniques, have relegated discussions about psychotherapy mostly to reviews about the history of treatment for autism. Even when psychotherapeutic work is suggested, it is typically only very structured supportive counseling for older and high functioning children and adolescents that is considered. This paper argues that there is a central role for psychotherapy for children with pervasive developmental disorders, and that psychotherapeutic interventions should begin at a younger, rather than older age.

4.4.24. Kravits, T.R., Kamps, D.M., Kemmerer, K., Potucek, J. "Brief report: increasing communication skills for an elementary-aged student with autism using the Picture Exchange Communication System." *J Autism Dev Disord* 2002 Jun;32(3):225-30.

University of Kansas, Juniper Gardens Children's Project, Kansas City 66101, USA.

The purpose of this study was to examine the effects of the Picture Exchange Communication System (PECS) on the spontaneous communication skills of a 6-year-old girl with autism across her home and school environments. The effects of the PECS were also examined for social interaction. Results indicated increases in spontaneous language (i.e., requests and comments) including use of the icons and verbalizations across those settings in which PECS was implemented. Intelligible verbalizations increased in two of three settings, and changes in peer social interaction were noted in one of the two school settings.

4.4.25. Hoch, H., McComas, J.J., Johnson, L., Faranda, N., Guenther, S.L. "The effects of magnitude and quality of reinforcement on choice responding during play activities." *J Appl Behav Anal* 2002 Summer;35(2):171-81.

The Graduate Center, CUNY, USA.

Three boys with autism participated in a study of the effects of magnitude and quality of reinforcement on choice responding. Two concurrent response alternatives were arranged: (a) to play in an area where a peer or sibling was located, or (b) to play in an area where there was no peer or sibling. During one condition, the magnitude (i.e., duration of access to toys) or quality (level of preference) of reinforcement provided for both responses was equal. During the other condition, the magnitude or quality of reinforcement was relatively greater for choosing the play area where the peer or sibling was located than the area where the peer or sibling was not located. Results showed that after repeated exposure to the unequal magnitude or quality condition, the participant increasingly allocated his responses to the play area where the peer or sibling was located. For 2 participants, this pattern of responding was maintained in the subsequent equal magnitude or quality condition. Overall, the analysis suggests that the dimensions of magnitude and quality of reinforcement can be arranged to influence choice responding in favor of playing near a peer or sibling rather than playing alone.

4.4.26. Pearlman-Avnion, S., Eviatar, Z. "Narrative analysis in developmental social and linguistic pathologies: dissociation between emotional and informational language use." *Brain Cogn* 2002 Mar-Apr;48(2-3):494-9.

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This study examined the use of emotional and informational aspects of language in populations that demonstrate developmental social-emotional and linguistic pathologies. We tested high-functioning autistic (HFA) individuals because this group reveals deficiencies in social-emotional and informative aspects of language as well as abnormalities in sociability. We tested Williams syndrome (WS) individuals because of the claim that the social-emotional aspects of language use and sociability are differentially preserved in the context of mental retardation. We compared the performance of these two groups with two groups of control children (7- and 11-year-olds). All of the participants viewed

a slide show depicting an event and were asked to retell the story. These narratives were coded for emotional and informational elements. The results showed that on measures of emotional elements, the WS group patterned with the control groups and only the HFA participants received lower scores, while on the informational elements, the two pathological groups did not differ, and both were lower than the controls. The results suggest that the preservation of language among WS individuals is specific for the emotional aspects of language.

4.4.27. Chandler, S., Christie, P., Newson, E., Prevezer, W. "Developing a diagnostic and intervention package for 2- to 3-year-olds with autism: outcomes of the frameworks for communication approach." *Autism* 2002 Mar;6(1):47-69. Publication Types: Clinical Trial, Evaluation Studies.

Early Years Diagnostic Centre, Nottingham, UK.

The aim of the research was to develop and evaluate a model of good practice which would make an explicit link between diagnosis and intervention, and so give parents a very clear rationale for the autism-specific yet individualized programme that they were carrying out. It employed an action research design, which essentially is responsive to participants, thus developing a user-friendly model of service. The programme was based on the developmental perspective that the pragmatics of language are the precursors of speech itself and enable both communication and relationship between child and parents. Since these are impaired in autism they should therefore be prioritized in early intervention. Ten children aged 1;10 to 2;9 at assessment, and with a diagnosis of autism, underwent an intervention based on home visits, modelling, workshops and written information, with parents as 'therapists' in naturally occurring situations. Within 18 months all children made substantial progress in social interaction and expressive communication, including gestural and verbal communication.

4.4.28. Corbett, B., Khan, K., Czapansky-Beilman, D., Brady, N., Dropik, P., Goldman, D.Z., Delaney, K., Sharp, H., Mueller, I., Shapiro, E., Ziegler, R. "A double-blind, placebo-controlled crossover study investigating the effect of porcine secretin in children with autism." *Clin Pediatr (Phila)* 2001 Jun;40(6):327-31. Publication Types: Clinical Trial, Randomized Controlled Trial.

Department of Pediatrics, Divisions of Pediatric Neurology, University of Minnesota, Minneapolis, MN, USA.

OBJECTIVES: A recent patient series reported the incidental findings of improved social and language skills in 3 children with autistic spectrum disorders after the administration of secretin, a peptide hormone. However, a subsequent study did not find evidence for a drug effect. Parents are seeking treatment with secretin despite the absence of empirical investigations demonstrating amelioration in autism symptomatology. In order to more precisely measure the effects of secretin, this study investigated the effect of a single intravenous dose of porcine secretin on 12 autistic children through a randomized, double-blind, placebo-controlled,

crossover study. Children were assessed on objective language and on social, neuropsychological, and gastrointestinal measures to evaluate drug effects. The study was conducted over a 16-week trial. The results indicated that significant differences were not observed on the majority of the dependent variables. Statistically significant differences were observed on measures of positive affect and activity level following secretin infusion. In general, the autistic children did not demonstrate the improvements described in the initial retrospective report.

4.4.29. Mostert, M.P. "Facilitated communication since 1995: a review of published studies." *J Autism Dev Disord* 2001 Jun;31(3):287-313. Publication Types: Review, Review, Tutorial.

Department of Early Childhood, Speech Language Pathology, & Special Education, Darden College of Education, Old Dominion University, Norfolk, Virginia 23529-0136, USA.

Previous reviews of Facilitated Communication (FC) studies have clearly established that proponents' claims are largely unsubstantiated and that using FC as an intervention for communicatively impaired or noncommunicative individuals is not recommended. However, while FC is less prominent than in the recent past, investigations of the technique's efficacy continue. This review examines published FC studies since the previous major reviews by Jacobson, Mulick, and Schwartz (1995) and Simpson and Myles (1995a). Findings support the conclusions of previous reviews. Furthermore, this review critiques and discounts the claims of two studies purporting to offer empirical evidence of FC efficacy using control procedures.

4.4.30. Tharpe, A.M., Fino-Szumski, M.S., Bess, F.H. "Survey of hearing aid fitting practices for children with multiple impairments." *Am J Audiol* 2001 Jun;10(1):32-40.

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The fitting of amplification on young children with multiple impairments in addition to hearing loss is a challenge faced regularly by audiologists. However, very little has been published on this topic in the audiological literature. The purpose of this survey was to document hearing aid fitting practices for this population within the United States. Specifically, audiologists who regularly serve children were asked to complete a series of questions on their educational preparation and their hearing aid selection, fitting, and verification practices for children with multiple impairments. For purposes of this survey, multiple impairments included vision impairment, mental retardation, physical impairment, and autism spectrum disorders. Findings from this survey suggest that children with special needs in addition to hearing loss are typically fit in the same way and with the same type of amplification as those with hearing loss only. In addition, differences were noted in hearing aid selection, fitting, and verification practices across work settings. Future directions and research needs are suggested.

4.4.31. Dennis, M., Lazenby, A.L., Lockyer, L. "Inferential language in high-function children with autism." *J Autism Dev Disord* 2001 Feb;31(1):47-54.

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Despite average verbal intelligence, high-function children with autism have social comprehension deficits that are expressed by how they use and understand language. In this paper, we explored the general hypothesis that high-function children with autism make some, but not all, of the pragmatic inferences necessary for successful communication, even when they have the ability to perform noninferential language tasks. We contrasted the ability of 8 high-function children with autism (each with Verbal IQ > 70) and typically developing children to use and understand: pragmatic inferences about given or presupposed knowledge in mental state words; pragmatic inferences about new or implied knowledge in mental state words; bridging inferences essential for coherence; elaborative inferences involved in enriching a communication by means of figurative language; and the intentional inferences involved in speech acts. High-function children with autism could define words and identify multiple meanings for ambiguous words. In understanding words for mental states, they made inferences from mental state verbs to given or presupposed knowledge. However, they failed to infer what mental state verbs implied in context; to make inferences about social scripts; to understand metaphor; and to produce speech acts, all of which are inferences that are the basis of successful social communication because they elaborate meaning or convey intentions.

4.4.32. Roberts, J.E., Mirrett, P., Burchinal, M. "Receptive and expressive communication development of young males with fragile X syndrome." *Am J Ment Retard* 2001 May;106(3):216-30.

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We prospectively examined the developmental trajectories of receptive and expressive communication skills of 39 young males, 20 to 86 months of age, with fragile X syndrome. Eight showed features characteristic of autism. Children were tested one to three times using a standardized language test. They showed marked delays in language development, but substantial individual variability. Participants acquired expressive language skills more slowly than receptive language over time, gaining receptive language at about half the rate expected for typically developing children and expressive language at one third the rate. Both cognitive skills and autistic characteristics of the young males with fragile X syndrome related to receptive and expressive communication development, but neither predicted the discrepancies between expressive and receptive language acquisition over time.

4.4.33. Kaiser, A.P., Hester, P.P., McDuffie, A.S. "Supporting communication in young children with developmental disabilities." *Ment Retard Dev Disabil Res Rev* 2001;7(2):143-50. Publication Types: Review, Review, Tutorial.

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The behavior of parents, adult caregivers, and peers comprises the critical features of community support for the development of communication in young children with developmental disabilities. In a bio-ecological model of development, communication development is the result of the interactions of individuals with specific characteristics, in particular contexts over time. From the perspective of this model, foundational findings of intervention research to current views of communication development in children with developmental disabilities are summarized. The contributions of individual child characteristics to child-caregiver interactions that support language development are illustrated based on research with children who have autism, Williams syndrome, Down syndrome, and children who use augmentative communication systems. Parent-child interaction and the quality and quantity of parent talk are discussed as factors in children's language development. The effects of young children's delayed language on their interactions with peers, the contributions of peers to children's language learning and use, and the critical features of classroom settings that support child language development are reviewed. MRDD Research Reviews 7:143-150, 2001. Copyright 2001 Wiley-Liss, Inc.

4.4.34. Conti-Ramsden, G., Botting, N., Simkin, Z., Knox, E. "Follow-up of children attending infant language units: outcomes at 11 years of age." *Int J Lang Commun Disord* 2001 Apr-Jun;36(2):207-19.

Human Communication and Deafness, School of Education, University of Manchester, Oxford Road, Manchester M13 9PL, UK. gina.conti-ramsd@man.ac.uk

A large cohort of 242 children who had been attending infants language units at 7 years of age was followed up when the children were in their final year of primary school. Two hundred (83%) of the children were reassessed at 11 years of age on a wide battery of language and literacy measures, on a test of non-verbal ability, an autism checklist and a communication checklist. In total, 89% of children still scored < 1 SD from the mean on at least one test of language and the majority (63%) scored poorly on three or more assessments demonstrating widespread difficulties. Compared with non-verbal abilities at 7 years of age, a large proportion of the cohort also performed poorly on performance IQ subtests (28%). A further 10 children scored highly on a checklist for autistic spectrum disorder. Thus, only 115 (58%) children could be said to meet criteria for specific language impairment. A small group of 16 children appeared to have entirely resolved their difficulties. These outcomes and their implications for education and long-term impact of the disorder are discussed.

4.4.35. Aldred, C., Pollard, C., Adams, C. "Child'sTalk – for children with autism and pervasive developmental disorder." *Int J Lang Commun Disord* 2001;36 Suppl:469-74.

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A research assessment protocol and early intervention approach designed for use by multi-disciplinary professionals with children who have the severe social communication deficits of early autism and pervasive developmental disorder (PDD) are described. The assessment analyses the specific pattern of social communication impairment in each child and defines the characteristics of the dyadic communication between parent and child. The intervention aims to identify facilitative strategies, using video feedback, which lead to close interpersonal interaction between the child and their parents. Parents can reflect on their own interaction and identify which strategies successfully engage their child. Child'sTalk aims to facilitate adaptations to the child's level of communication by sensitively and finely tuning the interaction and mutual sharing of intentions as a fundamental agent for the emergence of communication.

4.4.36. Forbes, J., Welbon, H. "Teacher/therapist collaboration: a Scottish higher education institution development." *Int J Lang Commun Disord* 2001;36 Suppl:417-22.

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The collaborative work is described of a principal speech and language therapist (SLT) and a lecturer in a college of education in Scotland in writing and evaluating a Post Graduate Award Scheme (PGAS) module. This was in response to Her Majesty's Inspectorate's (HMI) (1996) recommendation that teacher education institutions should 'consider the in-service and post-graduate training needs of those working with pupils with language and communication disorders and autism'. Official Scottish Executive Education Department (SEED) statements were examined by analysing HMI (1996) and subsequent official documents. Higher educational (HE) institution statements were read in the PGAS handbook and in the module descriptor (Northern College 1998). Accounts of change are described in the thinking and practice of course members as a result of the module and the implications for future module development are considered.

4.4.37. Liddle, K. "Implementing the picture exchange communication system (PECS)." *Int J Lang Commun Disord* 2001;36 Suppl:391-5. Publication Types: Evaluation Studies.

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PECS was developed in Delaware, USA over 10 years ago by Bondy and Frost (1994a). Over the last two years PECS has been introduced to this country and has raised a great deal of interest in people working in the field of autistic spectrum disorders (ASD). This paper will address some of the issues

that arose during the establishment of PECS in one special school. Changes seen in 21 children with severe learning difficulties who have been taught to use PECS are reported and the use of PECS with children who do not have an ASD is discussed.

4.4.38. Shinnar, S., Rapin, I., Arnold, S., Tuchman, R.F., Shulman, L., Ballaban-Gil, K., Maw, M., Deuel, R.K., Volkmar, F.R. "Language regression in childhood." *Pediatr Neurol* 2001 Mar;24(3):183-9

Department of Neurology, the Comprehensive Epilepsy Management Center at Montifiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, USA.

Language regression is observed both in autistic regression and as part of acquired epileptic aphasia (Landau-Kleffner Syndrome). We prospectively identified 177 children with language regression at four major medical centers, and their clinical characteristics were recorded. Their mean age at regression was 22.8 months. The mean time-to-specialist referral was 38 months of age. Most children (88%) met criteria for autism or manifested autistic features. Males ($P = 0.02$) and children less than 3 years of age who regressed ($P = 0.016$) had a higher probability of developing autistic behaviors. Seizures were more common in children who regressed after they reached 3 years of age ($P < 0.001$), and children with seizures were less likely to have associated autistic regression ($P < 0.001$). Electroencephalogram abnormalities were reported in 37% of patients and were more common in children with seizures ($P < 0.001$). At last follow-up, language function was impaired in 88% of the children, although some improvement was noted in 57%. We conclude that the loss of previously acquired language at any age, even if that language only includes a few words or communicative gestures, is often associated with a more global regression in cognition and/or behavior and has serious implications for future function. Early identification and referral of these children is necessary to allow for diagnosis and intervention.

4.4.39. Bara, B.G., Bucciarelli, M., Colle, L. "Communicative abilities in autism: evidence for attentional deficits." *Brain Lang* 2001 May;77(2):216-40.

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Although there are many theories about autism, something all of them agree upon is that autistics are impaired in the ability to communicate. The explanation is either their incapacity to attribute mental states to others or the interference of irrelevant stimuli with the access and processing of the communication (low). Our study on mute autistic children aims to investigate their communicative ability in order to bring some new evidence on the debate. We used an experimental technique that allows autistic children to access and process the communicative acts in a familiar context for as long as needed. The experimental results show that our sample of autistic children performs as well as the control group of normal children in dealing with direct, indirects, ironies, deceptions, and recoveries of failure.

Independent of their respective difficulty, the felicitous outcome of any of these acts requires the capacity to attribute an adequate communicative intention to the actor. Moreover, our results show that, contrary to the established findings in the literature, autistics' performance in the standard false belief task, a task that requires one to understand the mental states of other people, is equivalent to the performance of normal subjects. We argue that an attentional deficit affects the communicative performance of autistics in experiments where classic methodologies are used; with the proper methodology, we can access the unexplored world where mute autistic children also communicate. As far as we know, this is the first systematic experiment on pragmatic abilities in mute autistic children. Indeed, our work shows that tests and methodologies which help to focus on the communicative task improve the autistics' performance with respect to those used in the literature. We conclude that the autistic communicative deficit is at the performance level and that it has an attentional nature. Copyright 2001 Academic Press.

4.4.40. Zapor, M., Murphy, F.T., Enzenauer, R. "Echolalia as a novel manifestation of neuropsychiatric systemic lupus erythematosus." *South Med J* 2001 Jan;94(1):70-2.

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"That tongue of yours, by which I have been tricked, shall have its power curtailed and enjoy the briefest use of speech." With these words, Hera, of Greek mythology, deprived the nymph Echo of spontaneous speech, constraining her instead to merely repeating the words of others. Echolalia, which derives from the word "echo," is disordered speech in which an individual persistently repeats what is heard. Echolalia has been described in patients with a number of neuropsychiatric illnesses including autism and Tourette's syndrome. Neuropsychiatric systemic lupus erythematosus (NPSLE) is a heterogeneous disease with protean manifestations that may occur in approximately 25% to 50% of patients with systemic lupus erythematosus (SLE). Although the most common manifestations include cognitive dysfunction (50%) and seizures (20%), NPSLE may also present as peripheral neuropathy (15%), psychosis (10%), or other central nervous system abnormalities. We report the case of a 57-year-old woman with SLE and echolalia.

4.4.41. Khalifa, S., Bruneau, N., Roge, B., Georgieff, N., Veillet, E., Adrien, J.L., Barthelemy, C., Collet, L. "Peripheral auditory asymmetry in infantile autism." *Eur J Neurosci* 2001 Feb;13(3):628-32.

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Difficulty in filtering relevant auditory information in background noise is one of the features of autism. Auditory filtering processes can be investigated at the peripheral level as they are hypothesized to involve active cochlear mechanisms which are regulated by the efferent activity of the medial olivocochlear (MOC) system. The aim of the

present work was therefore to assess these peripheral auditory processes in 22 children and adolescents with autism compared with age- and gender-matched normal controls. Active cochlear mechanisms were evaluated with transiently evoked otoacoustic emissions (TEOAEs) and MOC system efficiency was assessed via TEOAEs which are decreased when stimulating the contralateral ear with noise. The MOC system evaluation was performed on 18 of the 22 children. In both studies, results were analysed according to age (from 4 to 10 years and from 11 to 20 years). The main result concerns the asymmetry of the efferent system which differs in individuals with autism. Several neural processes might be hypothesized as involved in the results obtained as the MOC system which originates in the brainstem received regulating controls from upper brain structures including auditory cortex. Lateralization abnormalities at the auditory periphery may reflect indirectly a problem at a higher level of auditory processing. A second important result shows a decrease in TEOAE amplitude with age, in patients, that may correspond to a decrease in hearing sensitivity.

4.4.42. Sherer, M., Pierce, K.L., Paredes, S., Kisacky, K.L., Ingersoll, B., Schreibman, L. "Enhancing conversation skills in children with autism via video technology. Which is better, "self" or "other" as a model?" *Behav Modif* 2001 Jan;25(1):140-58.

University of California, San Diego, USA.

The present study was designed to compare the efficacy of "self" versus "other" video-modeling interventions. Five children with autism ranging in age from 4 to 11 were taught to answer a series of conversation questions in both self and other video-modeled conditions. Results were evaluated using a combination of a multiple baseline and alternating treatments design. Three out of the five participants performed at levels of 100% accuracy at posttreatment. Results indicated no overall difference in rate of task acquisition between the two conditions, implying that children who were successful at learning from video in general, learned equally as well via both treatment approaches. Anecdotal evidence suggested that participants who were successful with video treatment had higher visual learning skills than children who were unsuccessful with this approach. Results are discussed in terms of a visual learning model for children with autism.

4.4.43. Jolliffe, T., Baron-Cohen, S. "Linguistic processing in high-functioning adults with autism or Asperger's syndrome. Is global coherence impaired?" *Psychol Med* 2000 Sep;30(5):1169-87.

Department of Experimental Psychology, University of Cambridge.

BACKGROUND: Linguistic processing was explored in normally intelligent adults with either autism or Asperger's syndrome, to test if global coherence was impaired. Global coherence is the ability to establish causal connections and interrelate local chunks into higher-order chunks so that most linguistic elements are linked together thematically. Since individuals with autism are hypothesized to have weak central

coherence then one would predict that the clinical groups would have difficulty integrating information globally so as to derive full meaning. **METHODS:** Two experiments were designed to test global coherence. Experiment 1 investigated whether individuals on the autism spectrum condition could arrange sentences coherently. Experiment 2 investigated whether they were less able to use context to make a global inference. **RESULTS:** The clinical groups were less able to arrange sentences coherently and use context to make a global inference. **CONCLUSIONS:** The results suggest that individuals on the autism spectrum have impaired global coherence. Arranging sentences and making global inferences correlated highly, suggesting that central coherence may be a unitary force in these different tasks. Of the two clinical groups, the autism group had the greater deficit. The effect that such a deficit would have on one's daily life is discussed, along with possible explanations for the clinical groups' greater difficulty, and suggestions for future research.

4.4.44. Pepperberg, I.M., Sherman, D. "Proposed use of two-part interactive modeling as a means to increase functional skills in children with a variety of disabilities." *Teach Learn Med* 2000 Fall;12(4):213-20.

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PURPOSE: Many behavior modification and intervention programs are based on operant procedures developed for animal subjects, but few use modeling procedures in which one student observes interactions between two proficient trainers. We show how such procedures, which successfully trained Grey parrots (*Psittacus erithacus*) to produce and comprehend elements of human language, can be adapted for use with children with three types of disabilities: (a) autism with limited social and language skills, (b) developmental delay with physical handicaps and lack of language skills, and (c) hyperactivity with impaired cognitive and social skills. **SUMMARY:** Children were evaluated before entering the program and outcomes were recorded to determine improvement levels. No child reached totally normative (physical age-appropriate) levels, but all significantly improved their social and communication skills and use of contextually appropriate behavior. **CONCLUSIONS:** A two-trainer modeling system can be a valuable intervention tool for children whose disabilities involve social and communicative skills.

4.4.45. Chin, H.Y., Bernard-Opitz, V. "Teaching conversational skills to children with autism: effect on the development of a theory of mind." *J Autism Dev Disord* 2000 Dec;30(6):569-83.

Department of Social Work and Psychology, National University of Singapore, Singapore.

This research examined whether children with autism could be trained to improve their conversational skills and whether this led to changes in standard tests of theory of mind (ToM). Three high-functioning children with autism participated in a multiple baseline across participants design. The children

were taught how to initiate a conversation, take turns during conversation, listen attentively, maintain a conversation topic, and change a conversation topic appropriately. The children were tested for ToM using False Belief tasks before and after training sessions. Results indicate that the amount of shared interest exhibited by the children with autism during conversation with their caregivers increased during training sessions. The children also made more responses that were appropriate to the context of the conversation. Performance on the False Belief tasks remained constant throughout the study. Results are discussed with respect to the implications of results of performance in standard ToM tasks.

4.4.46. Charlop-Christy, M.H., Le, L., Freeman, K.A. "A comparison of video modeling with in vivo modeling for teaching children with autism." *J Autism Dev Disord* 2000 Dec;30(6):537-52.

Department of Psychology, Claremont McKenna College, California 91711, USA.

The present study was designed to compare the effectiveness of video modeling with in vivo modeling for teaching developmental skills to children with autism. A multiple baseline design across five children and within child across the two modeling conditions (video and in vivo) and across tasks was used. Each child was presented two similar tasks from his or her curriculum; one task was used for the video condition, while the other was used for the in vivo condition. Video modeling consisted of each child watching a videotape of models performing the target behavior, whereas in vivo modeling consisted of the children observing live models perform the target behavior. After the observations, children were tested for acquisition and generalization of target behaviors. Results suggest that video modeling led to faster acquisition of tasks than in vivo modeling and was effective in promoting generalization. Results are discussed in terms of video modeling's motivating and attention maintaining qualities.

4.4.47. Wimpory, D.C., Hobson, R.P., Williams, J.M., Nash, S. "Are infants with autism socially engaged? A study of recent retrospective parental reports." *J Autism Dev Disord* 2000 Dec;30(6):525-36.

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The purpose of this study was to identify the specific aspects of social engagement that distinguish infants with autism from infants of similar age and developmental level who do not have autism. Ten parents of preschoolers with autism and 10 parents of matched children without autism were given a semistructured interview, the Detection of Autism by Infant Sociability Interview (DAISI), which elicits reports on whether 19 aspects of social engagement characteristic of typically developing infants were present at some time during the child's first 24 months. The reports of infants with autism differed from those of the control group on 16 items. Findings suggest that infants with autism have marked limitation in

both person-to-person and person-person-object social engagement, in keeping with the theory that autism involves impairments in primary as well as secondary intersubjectivity (Hobson, 1993a).

4.4.48. Gergely, G. "Reapproaching Mahler: new perspectives on normal autism, symbiosis, splitting and libidinal object constancy from cognitive developmental theory." *J Am Psychoanal Assoc* 2000;48(4):1197-228.

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Margaret Mahler's seminal work on the psychological birth of the infant has generated more critical discussion than most other psychoanalytic theories of early development. But while the empirically, theoretically, and methodologically based criticisms of Mahler's theory are generally justified, her critics fail at times to consider some of the intriguing and creative insights that her theoretical formulations tried to capture. This paper attempts to reformulate these insights using the new conceptual tools that current cognitive developmental theory provides. Mahler's stage of normal autism is reconsidered in the light of contingency detection theory as an initial phase of primary preoccupation with self-generated perfectly response-contingent stimulation. Her concept of normal symbiosis is recast with the help of attachment theory's views on homeostatic regulation and the social biofeedback model of affect-reflective mirroring interactions with parents. Finally, her ideas about the development of splitting and libidinal object constancy are reconsidered according to recent theories of early representational development and mentalization.

4.4.49. Mudford, O.C., Cross, B.A., Breen, S., Cullen, C., Reeves, D., Gould, J., Douglas, J. "Auditory integration training for children with autism: no behavioral benefits detected." *Am J Ment Retard* 2000 Mar;105(2):118-29. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Auditory integration training and a control treatment were provided for 16 children with autism in a crossover experimental design. Measures, blind to treatment order, included parent and teacher ratings of behavior, direct observational recordings, IQ, language, and social/adaptive tests. Significant differences tended to show that the control condition was superior on parent-rated measures of hyperactivity and on direct observational measures of ear-occlusion. No differences were detected on teacher-rated measures. Children's IQs and language comprehension did not increase, but adaptive/social behavior scores and expressive language quotients decreased. The majority of parents (56%) were unable to report in retrospect when their child had received auditory integration training. No individual child was identified as benefiting clinically or educationally from the treatment.

4.4.50. Dawson, G., Watling, R. "Interventions to facilitate auditory, visual, and motor integration in autism: a review of the evidence." *J Autism Dev Disord* 2000 Oct;30(5):415-21. Publication Types: Review, Review, Tutorial.

Center on Human Development and Disability, University of Washington, Seattle 98195, USA.

Evidence is reviewed on the prevalence of sensory and motor abnormalities in autism and the effectiveness of three interventions designed to address such abnormalities—sensory integration therapy, traditional occupational therapy, and auditory integration training. Although sensory processing and motor abnormalities are neither universal nor specific to autism, the prevalence of such abnormalities in autism is relatively high. There is, however, little controlled research on the effectiveness of interventions designed to address these abnormalities. Four objective outcome studies of sensory integration therapy were identified. These were of such small scale that no firm conclusions regarding efficacy could be made. No empirical studies of traditional occupational therapy in autism were found. Five studies of auditory integration training were found. Results of these studies provided no, or at best equivocal, support for the use of auditory integration training in autism.

4.4.51. Koegel, L.K. "Interventions to facilitate communication in autism." *J Autism Dev Disord* 2000 Oct;30(5):383-91.

University of California, Santa Barbara, USA.

The purpose of this article is to discuss research opportunities arising from the current literature in the area of communication. Six general themes are discussed, including (a) increasing spontaneity, initiations, and the variety of functions of language verbal and nonverbal children with autism exhibit; (b) assessing and teaching precursors relating to positive outcome; (c) the importance of family involvement in intervention programs; (d) best practices for implementation of communicative interventions; (e) the interrelationship between language and other behavioral symptoms of autism; and (f) the social and pragmatic use of language. These areas are discussed in terms of improving assessment and intervention practices to produce greater long-term communicative outcomes for individuals with autism.

4.4.52. Kamio, Y., Toichi, M. "Dual access to semantics in autism: is pictorial access superior to verbal access?" *J Child Psychol Psychiatry* 2000 Oct;41(7):859-67.

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The main aim of the present study was to compare pictures and words with respect to access to semantic systems in autism using a semantic priming paradigm. A word completion task was conducted using both within-modality (word word, WW) and cross-modality (picture word, PW) conditions on a group of high-functioning adolescents and adults with autism (N = 20) and a control group (N = 20)

matched on chronological age, mental age, Verbal IQ and Performance IQ. Both groups showed semantic priming effects in both modality conditions, generating significantly more responses for related prime-target pairs than for unrelated pairs. Although the control group performed similarly on both priming tasks, the autistic group performed significantly better on a PW task than on a WW task. These findings suggest the possible advantage of pictures over words in access to semantics in autism. The theoretical implications are discussed in terms of functional asymmetry between verbal and pictorial semantic operations that may be specific to autism.

4.4.53. Boucher, J., Lewis, V., Collis, G.M. "Voice processing abilities in children with autism, children with specific language impairments, and young typically developing children." *J Child Psychol Psychiatry* 2000 Oct;41(7):847-57.

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It is well established that people with autism have impaired face processing, but much less is known about voice processing in autism. Four experiments were therefore carried out to assess (1) familiar voice-face and sound-object matching; (2) familiar voice recognition; (3) unfamiliar voice discrimination; and (4) vocal affect naming and vocal-facial affect matching. In Experiments 1 and 2 language-matched children with specific language impairment (SLI) were the controls. In Experiments 3 and 4 language-matched children with SLI and young mainstream children were the controls. The results were unexpected: the children with autism were not impaired relative to controls on Experiments 1, 2 and 3, and were superior to the children with SLI on both parts of Experiment 4, although impaired on affect matching relative to the mainstream children. These results are interpreted in terms of an unexpected impairment of voice processing in the children with SLI associated partly, but not wholly, with an impairment of cross-modal processing. Performance on the experimental tasks was not associated with verbal or nonverbal ability in either of the clinical groups. The implications of these findings for understanding autism and SLI are discussed.

4.4.54. Sheinkopf, S.J., Mundy, P., Oller, D.K., Steffens, M. "Vocal atypicalities of preverbal autistic children." *J Autism Dev Disord* 2000 Aug;30(4):345-54.

Infant Development Center and Brown University School of Medicine, Providence, Rhode Island, USA.

This study was designed to evaluate the nature of early vocal behaviors in young children with autism. Recent methodological and conceptual advances in the study of infant preverbal vocalizations were used to provide a detailed examination of the vocal behavior of young preverbal children with autism and comparison children with developmental delays. Results revealed that children with autism did not have difficulty with the expression of well-formed syllables (i.e., canonical babbling). However, children with autism did display significant impairments in vocal quality (i.e., atypical

phonation). Specifically, autistic children produced a greater proportion of syllables with atypical phonation than did comparison children. Consistent with prior reports, the children with autism also displayed a deficit in joint attention behaviors. Furthermore, the atypicalities in the vocal behavior of children with autism appeared to be independent of individual differences in joint attention skill, suggesting that a multiple process model may be needed to describe early social-communication impairments in children with autism. Data are discussed in terms of their implications for future theoretical and applied research, including efforts to enhance the specificity of early diagnostic procedures.

4.4.55. Stein, M.T., Dixon, S.D., Cowan, C. "A two-year-old boy with language regression and unusual social interactions." *J Dev Behav Pediatr* 2000 Aug;21(4):285-90.

University of California, San Diego School of Medicine, USA.

CASE: Jimmy, a 2 1/2-year-old boy, was seen for the first time by a new pediatrician after a recent family move. His mother made the appointment for a health supervision visit although she had concerns about his language and social skills. She stated that he spoke primarily with unintelligible sounds and often communicated by pointing with his finger. He spoke only 10 words that were clear enough to be understood. Jimmy's mother said that he could hear, but she was not sure whether he understood everything she said. Although he played at home with his 4-year-old brother, he typically played by himself when he was in the presence of other children. Jimmy's mother was asked if he had had a 2-year-old visit to a pediatrician and what the assessment was at that time. She said that his delayed development was discussed with the pediatrician, but she was reassured that he would progress during the following year. An uncomplicated full-term gestation was followed by a vaginal delivery without perinatal problems. Jimmy was a "calm" baby who was breastfed for the first 6 months of life. He sat at 7 months, pulled himself up to stand with support at approximately 9 months, and walked at 13 months. Transitions were always difficult for Jimmy; he screamed and was difficult to settle whenever cared for by someone other than his parents. He typically resists physical contact when children or adults approach him. His mother recalled that language emerged early. He acquired a significant number of words between 12 and 15 months of age. Jimmy apparently recognized letters when his parents were teaching the older sibling. At 15 months, Jimmy's language output regressed dramatically, and by 18 months, he no longer used words to communicate. Since then, he has spoken fewer than 10 single words. He mostly babbles and uses repetitions of the same sounds. The pediatrician inquired into family structure and life events at the time Jimmy lost language milestones. He was told that, at this time, the father, an engineer, changed his position in the company and began to travel extensively. Jimmy's mother thought that the absence of his father might be related to the language regression. She also noted that Jimmy seemed to have a stronger attachment for his father: "Jimmy has always been attracted to his father, and his brother seems to prefer me." The parents' marriage was strong and free of any major disharmony. During the

interview, the pediatrician noted that Jimmy played persistently with his set of small trains, repetitiously lining them up in order. He was not interested in other toys that were on the floor next to him. He ran around the trains, mostly on his toes, while making unintelligible sounds. He looked away when the pediatrician called his name and became agitated when his mother attempted to redirect his attention to the examination. The pediatrician, 4 years in practice after his residency, had never seen a child with Jimmy's pattern of development. That Jimmy's development was unusual in two domains was apparent to his pediatrician from the preceding information and brief observations. He asked himself what the next steps should be.

4.4.56. Trevarthen, C. "Autism as a neurodevelopmental disorder affecting communication and learning in early childhood: prenatal origins, post-natal course and effective educational support." *Prostaglandins Leukot Essent Fatty Acids* 2000 Jul-Aug;63(1-2):41-6. Publication Types: Review, Review, Tutorial.

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Colwyn Trevarthen, working on autism, discussed the importance of time, rhythm and temporal processing in brain function. The brains of new born infants show highly coherent and coordinated patterns of activity over time, and their rhythms are remarkably similar to those of adults. Since the cortex has not yet developed, this coordination must be subcortical in origin. The likely source is the emotional motor system. He noted that the cerebellum might regulate the intricate timing of the development and expression of emotional communication. He also pointed out that emotional and motivational factors have often been seriously neglected in psychology (largely owing to a misplaced focus on 'cognition' as some isolated entity) and emphasized the potential importance of empathetic support and music therapy in helping autistic children. Copyright 2000 Harcourt Publishers Ltd.

4.4.57. Howlin, P., Mawhood, L., Rutter, M. "Autism and developmental receptive language disorder—a follow-up comparison in early adult life. II: Social, behavioural, and psychiatric outcomes." *J Child Psychol Psychiatry* 2000 Jul;41(5):561-78.

Department of Psychology, St George's Hospital Medical School, London, UK.

This paper focuses on general social functioning in two groups of young men, one with autism and one with developmental receptive language disorders, who were first assessed at the ages of 7-8 years. At that time, although matched for nonverbal IQ (mean 92-93) and expressive language, the Language group showed significantly fewer social and behavioural problems. At follow-up, when aged on average, 23 to 24 years, the Autism group continued to show significantly more impairments in terms of stereotyped behaviour patterns, social relationships, jobs, and independence. However, problems in all these areas were also common in the Language

group. Many still lived with their parents, few had close friends or permanent jobs, and ratings of social interaction indicated abnormalities in a number of different areas. On a composite measure of social competence only 10% of the Language group was assessed as having severe social difficulties compared to 74% of the Autism group. Nevertheless, 65% were rated as having moderate social problems and only 25% were rated as being of near/normal social functioning. Two individuals in the Language group, but none in the Autism group, had also developed a florid paranoid psychosis in late adolescence. As in the follow-up of cognitive and linguistic functioning (see Mawhood et al., 2000, this volume, pp. 547-559), discriminant function analysis, which had clearly distinguished between the groups as children, now showed much greater overlap between them. Regression analysis indicated that although early language ability appeared to be related to outcome in the Autism group, there was little association between any measures of childhood functioning and prognosis in the Language group. Theoretically, these findings have implications for our understanding of the nature of autism and other pervasive language disorders, and of the relationship between them. Practically, they demonstrate the very persistent problems experienced by individuals with developmental language disorders, and their need for much greater help and support than is presently available.

4.4.58. Wilson, B.L., Smith, D.S. "Music therapy assessment in school settings: a preliminary investigation." *J Music Ther* 2000 Summer;37(2):95-117. Publication Types: Review, Review, Tutorial.

Western Michigan University, USA.

The present investigation was undertaken in response to music therapists working in school settings for information relating to the availability of music therapy assessments and the feasibility of standardizing an assessment instrument for music therapists to use in school settings. Five research questions were identified, and the music therapy literature was surveyed to compile responses to those questions. Three different online data bases (ERIC, PsycINFO, and Article 1st) were used, covering articles published between 1980 and 1997. Individual hand searches were done of the *Arts in Psychotherapy*, *Journal of Music Therapy*, *Journal of Research in Music Education*, *Journal of the International Association of Music for the Handicapped*, *Music Therapy and Music Therapy Perspectives*. The questions and responses were as follows: 1. Which music-based assessment tools are being used with children with disabilities? Little commonality in assessment tools being used by music therapists and researchers was discovered. Of the total 41 studies, 20 (49%) reported using a "named" or "titled" assessment tool, and in the remaining 51% of studies, the authors reported using an untitled, and usually experimenter-designed, original assessment tool. 2. Have certain assessments been used in more than one study? Very limited replication of existing assessments was found. Of the 16 "named" assessments, only 3 were found to be used in more than one research study. 3. Are the actual assessments published along with the articles

describing their use? Only 3 of the 20 studies using named assessments were published along with the journal article. Of the remaining 21 studies using original, experimenter-designed assessment tools, only 6 (28%) had the assessment instrument published with the article. 4. What is the primary purpose for using the assessment? Six primary purposes emerged from the review of the literature: to compare with data obtained from other assessment measures or from other populations (39%), as a baseline or pretest measure (29%), to determine eligibility for services or the receipt of treatment (12%), to determine the psychometric properties of the assessment (7%), suitability of the instrument for the given population (7%), and the identification of musical preferences (5%). 5. What are the musical or nonmusic elements being assessed? Musical elements were: music perception (37%), musical aptitude (29%), musical preferences (12%), and attention to/enjoyment of music (2%). Nonmusical behaviors/responses were: self-expression (10%), motor responses (10%), behavioral responses (7%), cognitive development (2%), and acts of communication (2%). 6. What subject populations are being assessed? Subject populations were: children with developmental disabilities/mental retardation (44%), children with autism (10%), children with hearing impairments (17%), "psychiatric" clients or emotionally disturbed (22%), individuals described as "handicapped" (5%), individuals with physical disabilities (2%), and a student with a speech impairment (2%). Nondisabled individuals were also included in 12 of the aforementioned studies.

4.4.59. Craig, J., Baron-Cohen, S. "Story-telling ability in children with autism or Asperger syndrome: a window into the imagination." *Isr J Psychiatry Relat Sci* 2000;37(1):64-70.

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BACKGROUND: Autism spectrum conditions are diagnosed on the basis of impaired imagination. The present study used a totally free story-telling method to assess if narratives produced by children with autism or Asperger Syndrome (AS) contained fewer imaginative events. **METHOD:** In Condition 1, children were offered an imaginary theme and asked to elaborate a story. In Condition 2, they were offered a reality-based theme with the same instructions. Comparison groups included 13 children with autism, 14 children with AS, 15 children with moderate learning difficulties (MLD), and 14 normally developing children. The non-autistic controls had a verbal mental age (VMA) either equivalent or lower than the autism and AS groups. **RESULTS:** Both the children with autism and AS were less likely to introduce imaginary elements into their stories in Condition 2, though the children with AS were more able to produce imaginative narratives than children with autism in Condition 1. **CONCLUSIONS:** This study provides experimental evidence for imaginative impairments in story-telling in children with autism spectrum conditions. These are discussed in terms of two cognitive theories: executive dysfunction and theory of mind. **LIMITATIONS:** In this study it was not possible to match the children with autism and AS with each other on VMA, as the children with autism were not as high-functioning. Future

research could examine VMA matched groups of autism and AS.

4.4.60. Kobayashi, R. "Affective communication of infants with autistic spectrum disorder and internal representation of their mothers." *Psychiatry Clin Neurosci* 2000 Apr;54(2):235-43.

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We have been examining the developmental process of affective communication in infants with autistic spectrum disorders from the viewpoint of relationship disturbance through our developmental and psychopathological studies on autism. In particular, the role of internal representation of the mother in the process of development of affective communication is discussed through the presentation of two cases diagnosed as autistic spectrum disorder in early infancy. In these cases, we postulate approach-avoidance motivational conflict as the primary factor impeding development of affective communication, focusing therapeutic intervention on this perspective. As a result, attachment behavior was remarkably improved in the children, but affective communication with their mothers was not readily improved. Taking up the mothers' own internal representation in mother-infant psychotherapy, in particular, the mothers' problems in attachment behavior with their own mothers in infancy precipitated transition in the mothers' internal representation of their children, leading to active evolution in mother-child interaction and development in affective communication between mother and child. In this context, the basis and significance of internal representation of both parties being determinants in the quality of mother-child communication are discussed.

4.4.61. Morris, H.R., Thacker, A.J., Newman, P.K., Lees, A.J. "Sign language tics in a prelingually deaf man." *Mov Disord* 2000 Mar;15(2):318-20.

National Hospital for Neurology and Neurosurgery, London, UK.

Gilles de la Tourette syndrome is characterized by vocal and motor tics starting in childhood. Vocal tics may be either noises or words, and the vocal language tics may consist of obscenities (coprolalia) and repetitions of speech that has been heard (echolalia). We describe a prelingually deaf man who has the full array of tics seen in Gilles de la Tourette syndrome, but in whom vocal language tics are replaced by equivalent sign language tics. This is, to our knowledge, the first report of sign language tics in a person with prelingual deafness. The implications of this phenomenon for the separation between language and ideas in tics and the equivalence of sign language to spoken language is discussed.

4.4.62. Jambaque, I., Chiron, C., Dumas, C., Mumford, J., Dulac, O. "Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients." *Epilepsy Res* 2000 Feb;38(2-3):151-60.

Hospital Saint Vincent de Paul, Department of Pediatric Neurology, Paris, France.

Vigabatrin (VGB) has demonstrated high efficacy in infantile spasms (IS) due to tuberous sclerosis. Our first objective was to evaluate the cognitive long term effect outcome of children whose refractory spasms definitely disappeared when VGB was given as an add on drug. Our second objective was to determine the response of generalized epilepsy (infantile spasms) compared to partial epilepsy on cognitive impairment. A non selected series, of 13 children underwent psychometric and behavioural evaluation before VGB initiation at a mean of 3 years on VGB treatment. Eight of them could perform detailed neuropsychological tests at follow-up. Seven had infantile spasms (Group I), they all were spasm free before 2 years of age and five remained with rare partial seizures (mean age, 5.5 years). Six others had partial epilepsy without spasms (Group II) and five remained with rare seizures (mean age, 7.5 years). Patients of Group I experienced dramatic changes. Developmental quotient (DQ) significantly rose in six out of seven by ten to more than 45 points ($P = 0.03$) and autistic behaviour disappeared in five out of the six who presented with. The four tested children had normal verbal level after 5 years and could integrate at school but they remained with marked visuospatial disabilities. By contrast, patients of Group II remained with an unchanged DQ of about 60 so that both groups had similar DQ levels on follow-up. The cessation of spasms with VGB is therefore associated with significant improvement of cognition and behaviour in children with tuberous sclerosis. Controlling secondary generalization induced by infantile spasms seems to be a key factor for mental development.

4.4.63. Klein, S.K., Tuchman, R.F., Rapin, I. "The influence of premorbid language skills and behavior on language recovery in children with verbal auditory agnosia." *J Child Neurol* 2000 Jan;15(1):36-43 .

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Previous studies of children with Landau-Kleffner syndrome and related language-epilepsy syndromes have focused on the relationship of seizure control to language recovery. We examined the effect of premorbid language skills and behavior, as well as some characteristics of clinical seizures and electroencephalograms, on language recovery in a retrospective study of 67 children with the severe receptive and expressive language disorder, verbal auditory agnosia. Fifty-eight percent of these children had seizures, 76% were autistic, and 24% had a history of language regression after showing previously normal language skills. The duration of language loss was not influenced by the persistence of clinical seizures. Premorbid language and behavior were more predictive of language recovery in these children. Most children with normal early language (acquired verbal auditory agnosia) had onset of language loss after age 3 years, in contrast to those with abnormal early language. Children with acquired verbal auditory agnosia were more likely to show

fluctuations in language skills than those in other groups. Autistic children were more likely to begin having seizures before age 3 years, and had a longer duration of language loss and lower educational placement at time of last follow-up than those with normal behavior. This study emphasizes the importance of assessing premorbid language and behavior in predicting recovery of language skills in children with language-epilepsy syndromes.

4.4.64. Avikainen, S., Kulomaki, T., Hari, R. "Normal movement reading in Asperger subjects." *Neuroreport* 1999 Nov 26;10(17):3467-70.

Brain Research Unit, Helsinki University of Technology, Finland.

Patients with autism and Asperger syndrome (AS) are impaired in mindreading and imitation skills. One possibility would be that their 'mirror neuron' system, which matches action execution and observation, does not function properly. To test this hypothesis we compared action-viewing related motor cortex functions in an AS group (one autistic and four AS subjects) and eight control subjects. In both groups viewing hand actions modified the neuromagnetic approximately 20 Hz oscillatory activity in the primary motor cortex to the same extent. Thus impaired mindreading and imitation skills found in AS and autism do not seem to result from dysfunction of the motor cortex part of the action execution/observation system.

4.4.65. Heaton, P., Hermelin, B., Pring, L. "Can children with autistic spectrum disorders perceive affect in music? An experimental investigation." *Psychol Med* 1999 Nov;29(6):1405-10.

Social Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, Denmark Hill, London.

BACKGROUND: Children with autistic spectrum disorders typically show impairments in processing affective information within social and interpersonal domains. It has yet to be established whether such difficulties persist in the area of music; a domain which is characteristically rich in emotional content. **METHODS:** Fourteen children with autism and Asperger syndrome and their age and intelligence matched controls were tested for their ability to identify the affective connotations of melodies in the major or minor musical mode. They were required to match musical fragments with schematic representations of happy and sad faces. **RESULTS:** The groups did not differ in their ability to ascribe the musical examples to the two affective categories. **CONCLUSIONS:** In contrast to their performance within social and interpersonal domains, children with autistic disorders showed no deficits in processing affect in musical stimuli.

4.4.66. Sabbagh, M.A. "Communicative intentions and language: evidence from right-hemisphere damage and autism." *Brain Lang* 1999 Oct 15;70(1):29-69. Publication Types: Review, Review, Tutorial.

University of Oregon, USA.

In this review article, it is argued that the wide range of communicative deficits that have been noted in both individuals with damage to the right cerebral hemisphere (RHD) and high-functioning individuals with autism may stem from difficulties appreciating the importance of their interlocutor's communicative intentions (CIs). It is also argued that the abnormal semantic development noted in infants with RHD and autism may be related to difficulties in appreciating CIs as well. Finally, it is suggested that the CIs hypothesis may provide an avenue for integrating a number of theoretical suggestions that have been made regarding the right hemisphere's contributions to communicative competence. Copyright 1999 Academic Press.

4.4.67. Barber, C.F. "The use of music and colour theory as a behaviour modifier." *Br J Nurs* 1999 Apr 8-21;8(7):443-8.

North Birmingham Community NHS Trust, Aston.

For many centuries various aspects of healing have been linked to the use of the arts, in particular music and colour because of their innate ability to bring about a mental, emotional and physical calmness. Although much has been written on the use of colour and music as relaxants specifically within a nursing/medical context, there appears to be little information available as to why music and colour have this calming effect. This article examines music and colour as relaxants by briefly describing the neurological and physical mechanisms that bring about the effect of relaxation. This brief exploration is placed within the context of learning disability care. The aim is to provide ideas for a more peaceful and relaxing environment for an adult with learning disabilities who also has autism and exhibits severe challenging behaviour. The results of a small case study and implications for other areas of nursing are discussed.

4.4.68. Case-Smith, J., Miller, H. "Occupational therapy with children with pervasive developmental disorders." *Am J Occup Ther* 1999 Sep-Oct;53(5):506-13.

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OBJECTIVE: Although the prevalence of children with pervasive developmental disorders (PDD) has increased, empirical data about the role and practices of occupational therapists have not been reported in the literature. This descriptive study investigated the practice of occupational therapists with children with PDD. **METHOD:** A survey was mailed to 500 occupational therapists in the Sensory Integration Special Interest Section or School System Special Interest Section of the American Occupational Therapy Association in eastern and midwestern United States. The valid return rate was 58% (292 respondents). The survey used Likert scale items to measure frequency of performance problems observed in children with PDD, performance areas addressed in intervention, perceived improvement in performance, and frequency of use of and competency in intervention approaches. **RESULTS:** The respondents primarily worked in schools and reported that in the past 5 years they had served an increasing number of children with

PDD. Most respondents provided direct services and appeared to use holistic approaches in which they addressed multiple performance domains. They applied sensory integration and environmental modification approaches most frequently and believed that they were most competent in using these approaches. Respondents who reported more frequent use of and more competence in sensory integration approaches perceived more improvement in children's sensory processing. Respondents who reported more frequent use of and more competence in child-centered play perceived more improvement in children's sensory integration and play skills.

4.4.69. Watling, R., Deitz, J., Kanny, E.M., McLaughlin, J.F. "Current practice of occupational therapy for children with autism." *Am J Occup Ther* 1999 Sep-Oct;53(5):498-505.

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OBJECTIVE: The purpose of this study was to examine the current practice patterns of occupational therapists experienced in working with children with autism spectrum disorders. **METHOD:** Occupational therapists experienced in providing services to 2-year-old to 12-year-old children with autism completed a mail questionnaire describing practice patterns, theoretical approaches, intervention techniques, and preferred methods of preparation for work with children with autism. **RESULTS:** Of those contacted, 72 occupational therapists met the study criteria and returned completed questionnaires. Practice patterns included frequent collaboration with other professionals during assessment and intervention. Intervention services were typically provided in a one-to-one format with the most common techniques being sensory integration (99%) and positive reinforcement (93%). Theoretical approaches included sensory integration (99%), developmental (88%), and behavioral (73%). Evaluations relied heavily on nonstandardized tools and clinical observations. Educational methods identified as most helpful were weekend workshops (56%) and on-the-job training (52%). **CONCLUSION:** This study clarified the nature of current occupational therapy practice patterns for 2-year-old to 12-year-old children with autism. Additional studies are needed to examine the efficacy of current evaluation and intervention methods, as well as to explore the relevance of available standardized assessments for this population.

4.4.70. Case-Smith, J., Bryan, T. "The effects of occupational therapy with sensory integration emphasis on preschool-age children with autism." *Am J Occup Ther* 1999 Sep-Oct;53(5):489-97.

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OBJECTIVE: Using single-subject research design, the effects of an occupational therapy intervention emphasizing sensory integration with five preschool children with autism were examined. **METHOD:** In the AB design, nonengagement, mastery play, and interaction were measured, using videotape clips of each child's free play in the preschool. Following a 3-

week baseline, an occupational therapist provided one-on-one sessions and consultation to teachers for 10 weeks. **RESULTS:** When baseline and intervention phases were compared, four children demonstrated decreased frequency of nonengaged behavior, and three demonstrated increased frequency of mastery (goal-directed) play. Improvements in frequency of interaction were minimal. **CONCLUSION:** The results support descriptions in the literature regarding the behavioral changes that children with autism can make when participating in intervention using a sensory integration approach.

4.4.71. Brasic, J.R. "Movements in autistic disorder." *Med Hypotheses* 1999 Jul;53(1):48-9. Publication Types: Review, Review, Tutorial.

Department of Psychiatry, Bellevue Hospital Center, New York University School of Medicine, 10016-6481, USA.

Autistic disorder, an extremely disabling syndrome with onset in early childhood, is associated with multiple comorbid conditions. Although autistic disorder is heterogeneous in its manifestations, there is a subgroup of individuals with autistic disorder who display movements that appear to be unique for the disorders. Hand flapping and a variety of movements termed stereotypies may be pathognomonic of autistic disorder. Therefore, identification of a movement disorder characteristic of autistic disorder may imply that the individual has autistic disorder.

4.4.72. el-Ghoroury, N.H., Romanczyk, R.G. "Play interactions of family members towards children with autism." *J Autism Dev Disord* 1999 Jun;29(3):249-58.

Department of Psychology, State University of New York at Binghamton, New York 13902-6000, USA.

The play interactions of family members towards children with autism were examined in the current study. Siblings, mothers, and fathers of nine families of a child with autism were observed in dyadic play interactions with the child. Results revealed that mothers and fathers exhibited more play behaviors towards children with autism than siblings, while the children with autism initiated more interactions towards siblings than towards parents. Vineland scale scores were correlated with parental behaviors and the initiations of children with autism towards parents. Results suggest that parents may compensate for their child's disability level by initiating more play interactions. Implications include teaching parents how to pace play interactions to allow children with autism to initiate play interactions.

4.4.73. Leung, A.K., Kao, C.P. "Evaluation and management of the child with speech delay." *Am Fam Physician* 1999 Jun;59(11):3121-8, 3135. Publication Types: Review, Review, Tutorial.

Alberta Children's Hospital and University of Calgary, Canada.

A delay in speech development may be a symptom of many disorders, including mental retardation, hearing loss, an

expressive language disorder, psychosocial deprivation, autism, elective mutism, receptive aphasia and cerebral palsy. Speech delay may be secondary to maturation delay or bilingualism. Being familiar with the factors to look for when taking the history and performing the physical examination allows physicians to make a prompt diagnosis. Timely detection and early intervention may mitigate the emotional, social and cognitive deficits of this disability and improve the outcome.

4.4.74. Robertson, J.M., Tanguay, P.E., L'Ecuyer, S., Sims, A., Waltrip, C. "Domains of social communication handicap in autism spectrum disorder." *J Am Acad Child Adolesc Psychiatry* 1999 Jun;38(6):738-45.

Department of Psychiatry, University of Louisville School of Medicine, KY, USA.

OBJECTIVE: To investigate whether specific "social communication" handicaps could be identified in autism spectrum disorder using the Autism Diagnostic Observation Schedule and to compare the results with those found in a previous factor-analysis study using the Autism Diagnostic Interview-Revised. **METHOD:** All subjects were evaluated with both instruments. J.R. and P.E.T. independently diagnosed autism, Asperger's disorder, or pervasive developmental disorder—not otherwise specified in 51 children. Items from the Autism Diagnostic Observation Schedule that represented social communication behaviors were factor-analyzed. **RESULTS:** Three factors were identified: joint attention, affective reciprocity, and theory of mind. These are the same social communication domains that were identified in the previous study. **CONCLUSIONS:** These 3 social communication domains have been discussed in the literature regarding normal development and in previous research on autism spectrum disorders. If these domains are replicated in larger sample sizes, they could be used to monitor the results of pharmacological and psychotherapeutic interventions in autism spectrum disorders.

4.4.75. Slevin, E., McClelland, A. "Multisensory environments: are they therapeutic? A single-subject evaluation of the clinical effectiveness of a multisensory environment." *J Clin Nurs* 1999 Jan;8(1):48-56. Publication Types: Clinical Trial, Controlled Clinical Trial.

School of Health Sciences University of Ulster, Newtownabbey, UK. JE.Slevin@ulst.ac.uk

This article reviews the current literature on multisensory therapy. Utilizing a single-subject quasi-experimental design, the therapeutic clinical effectiveness of multisensory therapy in promoting relaxation in a young man with learning disabilities is evaluated. Findings support the hypothesis that multisensory therapy can promote relaxation. It is concluded that multisensory environments are therapeutic, in that they can promote relaxation, and they may also have a place in the care of people with learning disabilities who display challenging behaviours.

4.4.76. Linderman, T.M., Stewart, K.B. "Sensory integrative-based occupational therapy and functional outcomes in young children with pervasive developmental disorders: a single-subject study." *Am J Occup Ther* 1999 Mar-Apr;53(2):207-13.

Mighty Oaks Children's Therapy Center, Albany, Oregon 97321, USA.

OBJECTIVE: This single-subject study explored the effects of sensory integrative-based occupational therapy provided in an outpatient clinic on the functional behaviors of two young children with pervasive developmental disorder (PDD) at home. **METHOD:** The participants were two 3-year-old boys with PDD. Before the study, the participants had not received a consistent program of sensory integrative-based occupational therapy. Before the baseline phase, three target behaviors were identified for each child, using an adapted version of Cook's revised Functional Behavior Assessment for Children with Sensory Integrative Dysfunction. These target behaviors were operationalized and used as repeated measures taken in the home during both the 2-week baseline and treatment phases. The treatment phase was 11 weeks for Participant 1 and 7 weeks for Participant 2. **RESULTS:** Both participants displayed significant improvements in the areas of social interaction, approach to new activities, response to holding or hugging, and response to movement. Decreases were noted in the frequency and duration of disruptive behaviors (e.g., high activity levels, aggressive behaviors), with an increase in functional behaviors, such as spontaneous speech, purposeful play, and attention to activities and conversation. Concurrent interventions that were not part of this study (e.g., initiation of speech therapy, preschool, vitamins) may have confounded these results. **CONCLUSIONS:** These findings support the application of sensory integrative-based occupational therapy as a part of the services provided to some children with PDD. Further research is needed to replicate these findings and to isolate the effects of sensory integrative-based occupational therapy because both participants were receiving other interventions at the time of this study.

4.4.77. Turner, M.A. "Generating novel ideas: fluency performance in high-functioning and learning disabled individuals with autism." *J Child Psychol Psychiatry* 1999 Feb;40(2):189-201.

University of Durham, UK. Michelle.Turner@durham.ac.uk

Tasks of fluency tap the ability to generate multiple responses spontaneously following a single cue or instruction. The present study compared the fluency performance of subjects with autism and clinical control subjects at two different levels of ability (high-functioning subjects with a verbal IQ of 76 or greater, and globally learning disabled subjects with a verbal IQ of 74 or below). A battery of tasks was employed to assess subjects' word fluency (for letters and semantic categories), ideational fluency (for uses of objects and interpretations of meaningless line drawings), and design fluency (for abstract meaningless designs). Subjects with autism showed reduced fluency for both the word and ideational fluency tasks,

generating significantly fewer responses than the clinical control subjects. Results were particularly striking for the ideational fluency tasks. On these tasks, autistic subjects produced very low response totals, with the performance of the high-functioning subjects with autism equivalent to that of the learning disabled subjects with autism and significantly inferior to that of the learning disabled control individuals. In contrast, the results of the design fluency paradigm paint a different picture. This paradigm revealed no significant difference in the quantity of designs generated by the subjects with autism and the control subjects but a clear qualitative difference, with the autistic group producing significantly higher rates of disallowed and perseverative responses. Whilst the results of the word and ideational fluency tasks are suggested to support the hypothesis that individuals with autism are impaired in the generation of novel responses and behaviour, the results of the design fluency task are equally consistent with an impairment in the regulation of behaviour through inhibition and/or monitoring. The implications of these findings for the study of executive function abilities in autism are discussed.

4.4.78. Rollins, P.R., Snow, C.E. "Shared attention and grammatical development in typical children and children with autism." *J Child Lang* 1998 Oct;25(3):653-73.

University of Texas at Dallas, Callier Center for Communication Disorders 75235, USA.

The two studies presented here explore the relationship between children's pragmatic skills and their growth in grammar. In study 1, thirty normally developing children were videotaped interacting with their parents at 1;2 and again at 2;7. Using correlational and regression techniques, we found that pragmatic accomplishments of MUTUAL ATTENTION, as well as mother's conversational style, explained 45% of the variance in grammar at 2;7. The second study investigated pragmatic-grammatical relationships with data from 6 high-functioning children with autism. To control for individual variation in skill level at the start of the study, within-individual growth rates for grammar were estimated as our outcome. The results substantiated those of study 1, in that pragmatic accomplishments within mutual attention predicted the per month growth rate in grammar. We interpret these findings as consistent with the position that the infant's social-pragmatic skills contribute to the acquisition of grammar.

4.4.79. Buffington, D.M., Krantz, P.J., McClannahan, L.E., Poulson, C.I. "Procedures for teaching appropriate gestural communication skills to children with autism." *J Autism Dev Disord* 1998 Dec;28(6):535-45.

Princeton Child Development Institute, Princeton, New Jersey, USA.

Four children with autism were taught to use gestures in combination with oral communication. Using a multiple-baseline across-responses design, intervention was introduced successively across three response categories containing gestures representative of attention-directing/getting,

affective, and descriptive behavior. Although none of the participants displayed appropriate gestural and verbal responses during baseline, all participants acquired this skill with the systematic implementation of modeling, prompting, and reinforcement. Generalization measures indicated that the children learned to respond in the presence of novel stimuli and a novel setting. Social validity measures revealed that the participants' behavior appeared more socially appropriate at the completion of the study than at the start of the study, and that the participants' behavior was indistinguishable from that of their typically developing peers.

4.4.80. Libby, S., Powell, S., Messer, D., Jordan, R. "Spontaneous play in children with autism: a reappraisal." *J Autism Dev Disord* 1998 Dec;28(6):487-97.

Department of Clinical Psychology, University of East Anglia, Norwich, United Kingdom.

Much controversy remains regarding the ability of children with autism to engage in spontaneous play. In this study children with autism, Down syndrome and typical development with verbal mental ages of approximately 2 years were assessed for play abilities at three data points. Even in this group of children with autism, who had relatively low verbal mental ages, symbolic play skills were not totally absent. However, it was possible to distinguish their pattern of play behaviors from the other two groups. Consequentially, it is argued that there are unusual features in early spontaneous play in children with autism and these atypical patterns are not restricted to their difficulties in the production of symbolic play. Such differences in early spontaneous play raise interesting questions about the etiology of autism, the direction of future research, and the theoretical models that can account for the condition.

4.4.81. Schepis, M.M., Reid, D.H., Behrmann, M.M., Sutton, K.A. "Increasing communicative interactions of young children with autism using a voice output communication aid and naturalistic teaching." *J Appl Behav Anal* 1998 Winter;31(4):561-78.

Western Carolina Center, Family, Infant, and Preschool Program, Morganton, North Carolina 28655, USA.

We evaluated the effects of a voice output communication aid (VOCA) and naturalistic teaching procedures on the communicative interactions of young children with autism. A teacher and three assistants were taught to use naturalistic teaching strategies to provide opportunities for VOCA use in the context of regularly occurring classroom routines. Naturalistic teaching procedures and VOCA use were introduced in multiple probe fashion across 4 children and two classroom routines (snack and play). As the procedures were implemented, all children showed increases in communicative interactions using VOCAs. Also, there was no apparent reductive effect of VOCA use within the naturalistic teaching paradigm on other communicative behaviors. Teachers' ratings of children's VOCA communication, as well as ratings of a person unfamiliar with the children, supported the contextual appropriateness of the

VOCA. Probes likewise indicated that the children used the VOCAs for a variety of different messages including requests, yes and no responses, statements, and social comments. Results are discussed in regard to the potential benefits of a VOCA when combined with naturalistic teaching procedures. Future research needs are also discussed, focusing on more precise identification of the attributes of VOCA use for children with autism, as well as for their support personnel.

4.4.82. Fisher, W.W., Kuhn, D.E., Thompson, R.H. **"Establishing discriminative control of responding using functional and alternative reinforcers during functional communication training."** *J Appl Behav Anal* 1998 Winter;31(4):543-60.

Neurobehavioral Unit, Kennedy Krieger Institute, Baltimore, Maryland 21205, USA.

Functional communication training (FCT) is a popular treatment for problem behaviors, but its effectiveness may be compromised when the client emits the target communication response and reinforcement is either delayed or denied. In the current investigation, we trained 2 individuals to emit different communication responses to request (a) the reinforcer for destructive behavior in a given situation (e.g., contingent attention in the attention condition of a functional analysis) and (b) an alternative reinforcer (e.g., toys in the attention condition of a functional analysis). Next, we taught the participants to request each reinforcer in the presence of a different discriminative stimulus (SD). Then, we evaluated the effects of differential reinforcement of communication (DRC) using the functional and alternative reinforcers and correlated SDs, with and without extinction of destructive behavior. During all applications, DRC (in combination with SDs that signaled available reinforcers) rapidly reduced destructive behavior to low levels regardless of whether the functional reinforcer or an alternative reinforcer was available or whether reinforcement for destructive behavior was discontinued (i.e., extinction).

4.4.83. Strain, P.S., Kohler, F. **"Peer-mediated social intervention for young children with autism."** *Semin Speech Lang* 1998;19(4):391-404; quiz 404-5; 424.

University of Colorado, School of Education, Denver, USA.

In this paper, we trace the history of peer-mediated intervention for young children with autism. Special attention is paid to outcomes achieved, implementation strategies, practicality, combining peer-mediation and naturalistic teaching, and overall conclusions from 20 years of study.

4.4.84. Koegel, L.K., Koegel, R.L., Carter, C.M. **"Pivotal responses and the natural language teaching paradigm."** *Semin Speech Lang* 1998;19(4):355-71; quiz 372; 424. Publication Types: Review, Review, Tutorial.

Autism Research Center Graduate School of Education, Psychology Clinic, University of California, Santa Barbara 93106-9490, USA.

This article discusses the identification of pivotal behaviors for maximizing the impact of intervention for children with autism. Language deficits are not likely to make sufficient improvement unless pivotal variables, such as motivation, are addressed in the design of intervention programs. Pivotal target behaviors related to such children's motivation to engage in social communication are discussed, and their integration into a Natural Language Teaching Paradigm is described. Of particular interest are variables related to child choice, the use of natural reinforcers, the interspersal of maintenance trials to build behavioral momentum, and reinforcing communicative attempts. When used in combination to motivate the children to engage in and initiate communicative interactions, the impact on development can be considerable in terms of rate of acquisition, generalization of gains, and normalization of language development.

4.4.85. Prizant, B.M., Wetherby, A.M. **"Understanding the continuum of discrete-trial traditional behavioral to social-pragmatic developmental approaches in communication enhancement for young children with autism/PDD."** *Semin Speech Lang* 1998;19(4):329-52; quiz 353; 424. Publication Types: Review, Review, Tutorial.

Center for Human Development, Brown University, Providence, Rhode Island, USA.

Clinicians are faced with the challenge of making informed decisions amidst heated debates over the most effective treatment approaches for young children with autism. This article provides a more specific focus to this debate by considering the practice of enhancing spontaneous language and related social-communicative abilities of young children with autism/pervasive developmental disorder (PPD). First, a historical perspective of the evolution of different approaches for enhancing communication and related abilities is presented, followed by a description of characteristics of the approaches. The approaches are described along a continuum from massed discrete trial, traditional behavioral to social-pragmatic, developmental. The current state of knowledge regarding the effectiveness of early services for children with autism/PDD is examined and conclusions are presented with consideration of the need for more meaningful outcome measures than are currently used for the next generation of outcome research.

4.4.86. Beversdorf, D.Q., Anderson, J.M., Manning, S.E., Anderson, S.L., Nordgren, R.E., Felopulos, G.J., Nadeau, S.E., Heilman, K.M., Bauman, M.L. **"The effect of semantic and emotional context on written recall for verbal language in high functioning adults with autism spectrum disorder."** *J Neurol Neurosurg Psychiatry* 1998 Nov;65(5):685-92.

Ohio State University Medical Centre, Department of Neurology, Columbus 43210, USA. beversdorf.2@osu.edu

OBJECTIVE: Several deficits have been proposed to account for cognitive impairment in autism including an inability to comprehend the perspectives of others ("theory of mind"),

an inability to process emotional information, and difficulty drawing together diverse information in context ("central coherence"). Because context (central coherence) and emotion can influence memory, a study was designed to show if autism spectrum disorder was associated with impaired utilisation of context and emotion in recall; and if impairments in theory of mind processing would influence recall in autism spectrum disorder. **METHODS:** Ten high functioning subjects with autism spectrum disorder and 13 age and IQ matched controls were tested using recall tests. In the first coherence memory test, subjects listened to a series of word lists that were in varying degrees of syntactic and semantic (coherent) order and were asked to recall the words. In the second coherence memory test, subjects listened to stories consisting of sentences that were, or were not, in logical (coherent) order. In the emotional memory test, the subjects listened to sentences that were highly emotional or non-emotional. In the theory of mind test, the subjects listened to stories requiring varying levels of understanding of the perspectives of others. **RESULTS:** There were no significant differences between groups in recall of coherent versus incoherent word lists, nor was there a significant difference between groups in recall of coherent versus incoherent stories. However, the control subjects recalled more of the emotional than non-emotional sentences, whereas the autism spectrum disorder group did not show such a difference. No significant difference existed in recall of stories requiring varying levels of understanding of the perspectives of others among subjects with autism spectrum disorder, and subjects with autism spectrum disorder did not differ from control subjects in the influence of theory of mind content on story recall. **CONCLUSION:** The study shows that memory in high functioning adults with autism spectrum disorder is facilitated by emotional content to a lesser degree than it is facilitated

by coherence. Therefore, impairments in emotional processing cannot be considered as simply an effect of the "weak central coherence" theory in autism spectrum disorder. Whereas the reasons for this emotional deficit are unknown, evidence of abnormalities of the limbic structures in autism spectrum disorder may provide an anatomical explanation.

4.4.87. Jocelyn, L.J., Casiro, O.G., Beattie, D., Bow, J., Kneisz, J. **"Treatment of children with autism: a randomized controlled trial to evaluate a caregiver-based intervention program in community day-care centers."** *J Dev Behav Pediatr* 1998 Oct;19(5):326-34. Publication Types: Clinical Trial, Randomized Controlled Trial.

Department of Pediatrics and Child Health, University of Manitoba, Canada.

This study reports on the results of a randomized controlled trial that evaluated a caregiver-based intervention program for children with autism in community day-care centers. Thirty-five preschool children with a DSM III-R diagnosis of autism or pervasive developmental disorder were randomized to an experimental or control group. Children in the experimental group were enrolled in day care and their parents and child care workers received a 12-week intervention consisting of lectures and on-site consultations to day-care centers. In addition, supportive work was undertaken with families. Control subjects received day care alone. In the experimental group, there were greater gains in language abilities, significant increases in caregivers' knowledge about autism, greater perception of control on the part of mothers, and greater parent satisfaction. We conclude that this research design demonstrated that the intervention was significantly superior to day care alone.

EDUCATIONAL

5.1. Mithaug, D.K., Mithaug, D.E. "Effects of teacher-directed versus student-directed instruction on self-management of young children with disabilities." *J Appl Behav Anal.* 2003 Spring;36(1):133-6. Publication Types: Evaluation Studies.

Teachers College, Columbia University, USA.
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In this study, students worked independently by setting goals, selecting assignments, and recording and evaluating their results after receiving one of two different types of self-management training. During teacher-directed training, the teacher set goals, assigned work, and recorded and evaluated results for students. During student-directed training, students performed those tasks themselves. The results indicated that students engaged in the self-management behaviors more frequently during independent work following student-directed instruction than following teacher-directed instruction.

5.2. Kielinen, M., Linna, S.L., Moilanen, I. "Some aspects of treatment and habilitation of children and adolescents with autistic disorder in Northern-Finland." *Int J Circumpolar Health.* 2002;61 Suppl 2:69-79.

Clinic of Child Psychiatry, University Hospital of Oulu, Oulu, Finland. marko.kielinen@autismiliitto.fi

Hospital records and data on the treatment/habilitation status of 187 children with autism aged 3-18 years were gathered from Northern Finland. The treatment programs and therapies varied, depending on the trained staff available. One-hundred and fifty-two (82.9%) children and adolescents with autism received more than one therapeutic intervention or specific training program. The most common therapies were physiotherapy as well as speech, occupational and music therapy. 43.9% of the children and adolescents with autism received specific training according to TEACCH (Treatment and Education of Autistic and related Communication-Handicapped Children), 10.2% according to Lovaas and 30.5% according to the Portage program. Antiepileptic medication had been prescribed to 23.9% and psychopharmacological interventions to 14.9% of the individuals with autistic disorder (AD). One hundred and seventy-eight subjects out of 187 showed some improvement on the Childhood Autism Rating Scale (CARS), even if no statistically significant difference was found between the outcome of the available habilitation methods.

5.3. Bolte, S., Feineis-Matthews, S., Leber, S., Dierks, T., Hubl, D., Poustka, F. "The development and evaluation of a computer-based program to test and to teach the recognition of facial affect." *Int J Circumpolar Health.* 2002;61 Suppl 2:61-8. Publication Types: Clinical Trial, Evaluation Studies, Randomized Controlled Trial.

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Autism is a chronic pervasive neurodevelopmental disorder characterized by the early onset of social and communicative impairments as well as restricted, ritualized, stereotypic behavior. The endophenotype of autism includes neuropsychological deficits, for instance a lack of "Theory of Mind" and problems recognizing facial affect. In this study, we report the development and evaluation of a computer-based program to teach and test the ability to identify basic facially expressed emotions. 10 adolescent or adult subjects with high-functioning autism or Asperger-syndrome were included in the investigation. A priori the facial affect recognition test had shown good psychometric properties in a normative sample (internal consistency: $r_{tt}=.91-.95$; retest reliability: $r_{tt}=.89-.92$). In a prepost design, one half of the sample was randomly assigned to receive computer treatment while the other half of the sample served as control group. The training was conducted for five weeks, consisting of two hours training a week. The trained individuals improved significantly on the affect recognition task, but not on any other measure. Results support the usefulness of the program to teach the detection of facial affect. However, the improvement found is limited to a circumscribed area of social-communicative function and generalization is not ensured.

5.4. Lee, R., McComas, J.J., Jawor, J. "The effects of differential and lag reinforcement schedules on varied verbal responding by individuals with autism." *J Appl Behav Anal.* 2002 Winter;35(4):391-402.

Queens College and The Graduate School and University Center of The City University of New York, USA.
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Variability has been shown to be a reinforceable dimension of behavior. One procedure that has been demonstrated to increase variability in basic research is the lag reinforcement schedule. On this type of schedule, a response is reinforced if it differs from a specified number of previous responses. Lag schedules are rarely used, however, for increasing response variability in applied settings. The purpose of the present study was to investigate the effects of a lag schedule of differential reinforcement on varied and appropriate verbal responding to social questions by 3 males with autism. A reversal design with a multiple baseline across subjects was used to evaluate the effects of the lag schedule. During baseline, differential reinforcement of appropriate responding (DRA) resulted in little or no varied responding. During the intervention, a Lag 1 requirement was added to the DRA (Lag 1/DRA) resulting in an increase in the percentage of trials with varied and appropriate verbal responding for 2 of the 3 participants. In addition, an increase in the cumulative number of novel verbal responses was also observed for the same 2 participants. These results are discussed in terms of reinforcement schedules that support variability, generalization, and potential stimulus control over varied responding.

5.5. Mandlawitz, M.R. "The impact of the legal system on educational programming for young children with autism spectrum disorder." *J Autism Dev Disord.* 2002 Oct;32(5):495-1. Publication Types: Review, Review, Tutorial.

MRM Associates, Washington, DC, USA.

Since 1990, State Educational Agency (SEA) and Local Educational Agency (LEA) policies and practices of educational programming for young children with autism have evolved in response to the due process system and court decisions. This has become an issue because of an increase in the identification of children with autism, reclassification of children previously reported under other disability categories, publicity about the competition between methodologies, parent advocacy for specific methodologies, shortages of qualified personnel, and the demand for due process to ensure appropriate services. A review is made of substantive and procedural issues presented in due process and court cases, the legal standards used by hearing officers and judges, and a synthesis of the case law. It is recommended that school districts consider legal standards as programs are designed, that programs fit the unique needs of the child, that programs ensure appropriate progress educationally and socially, and that communication between parents and school districts be open and honest so that the due process system is used as the last resort.

5.6. Turnbull, H.R. 3rd, Wilcox, B.L., Stowe, M.J. "A brief overview of special education law with focus on autism." *J Autism Dev Disord.* 2002 Oct;32(5):479-93.

The Beach Center on Families and Disability, University of Kansas, Haworth, Kansas 66045, USA. rud@ukans.edu

This article reviews the provisions of Individuals with Disabilities Education Act as they apply particularly to students with autism. It also refers to the antidiscrimination provisions of the Rehabilitation Act Amendments (Sec. 504) and to their relevance to students with autism. It attempts to answer specific questions posed by the National Academy of Science.

5.7. Jepsen, R.H., VonThaden, K. "The effect of cognitive education on the performance of students with neurological developmental disabilities." *NeuroRehabilitation* 2002;17(3):201-9.

Clinical Services, Bancroft NeuroHealth, Haddonfield, NJ 08033, USA. rjepsen@bnh.org

A cognitive education program was developed to facilitate acquisition of cognitive skills and address the learning deficits of adolescent students with neurological, developmental disabilities, and autism. This study examined the outcomes of incorporating mediated cognitive education into special education classrooms. Cognitive education provided cognitive training utilizing REHABIT materials through mediated teaching. Following a matched pair model, forty-six students were assigned to either a treatment or a control group. All students received weekly instruction in Individual Educational Program (IEP) goals. Curriculum areas included IEP objectives

in reading, math, social skills, health, science and social studies. Students in the control group received regular classroom instruction. Students in the treatment group participated in cognitive education one hour per week replacing thirty minutes of reading and thirty minutes of math. Pre and posttest comparisons on measures of intelligence, achievement and adaptive behavior showed those students in the treatment group attained higher scores across measures.

5.8. McDonald, B.C. "Recent developments in the application of the nonverbal learning disabilities model." *Curr Psychiatry Rep* 2002 Oct;4(5):323-30. Publication Types: Review, Review, Academic.

Neuropsychology Program, Department of Psychiatry, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA. Brenna.C.McDonald@dartmouth.edu

Since the original work of Myklebust et al., the concept of a syndrome of nonverbal learning disabilities (NLD) has undergone considerable development and expansion, most notably in the work of Rourke. These authors have proposed a model of white matter dysfunction, predominantly in the right cerebral hemisphere, which is thought to underlie the cognitive and behavioral impairments seen in individuals with NLD. Recent research has focused on assessing the applicability of Rourke's conceptualization of the NLD syndrome and the white matter model to various neurologic, neurodevelopmental, and genetic disorders. This paper highlights recent investigations of the NLD model with respect to velocardiofacial syndrome, Klinefelter syndrome, high functioning autism, neuro-fibromatosis type I, and metachromatic leukodystrophy, and also provides a brief discussion of recent conceptualizations of the NLD model in the broader context of disorders of social and emotional functioning, and of other novel avenues of NLD research.

5.9. Pring, L., Hermelin, B. "Numbers and letters: exploring an autistic savant's unpracticed ability." *Neurocase* 2002;8(4):330-7.

Psychology Department, Goldsmiths College, University of London, UK. l.pring@gold.ac.uk

This paper describes an individual with autism and high-level calendar calculation ability who could perform a set of unpracticed letter/number association tasks. The savant's performance was compared with that of two control participants, one a departmental secretary and the other a professor of mathematics. The facility with which the savant could master the rules governing the relationships between the series of items suggests that he possessed a flexibility of mental processing transcending his ability of calendar calculation. Furthermore, he could recalibrate previous knowledge to solve new hitherto unpracticed tasks. When presented with novel problems, the savant, unlike the mathematician, made no initial errors at all on any of the presented tasks, thereby indicating his fast and spontaneous recognition of new rules and of new relationships between items. It is concluded that a cognitive style of 'weak central coherence' as adopted by autistic savants may protect single

representations from being retained in the form of stable enduring wholes, and that such a segmentation strategy may allow for the transformation, reorganization and reconstruction of the relationship between single items of information.

5.10. Hideo, H., Yasuo, S. "Early intervention system for preschool children with autism in the community: the DISCOVERY approach in Yokohama, Japan." *Autism* 2002 Sep;6(3):239-57.

Yokohama Rehabilitation Center, Japan.
honda@yokohama.email.ne.jp

The article reports on DISCOVERY, a conceptual model for a clinical system of early detection and early intervention in cases of autism that has been implemented in Yokohama, Japan. The minimal requirements for this system are subsystems dealing with detection, diagnosis and intervention. Specific issues involving early diagnosis that complicate the design of the system are the seemingly contradictory considerations of early versus precise diagnosis, the undifferentiated recognition of a child's disorder on the part of the parents, and the difficulty of establishing cooperative working relationships among related facilities. To overcome these issues, an 'interface' linking consecutive subsystems is emphasized in the DISCOVERY model. A clinical system based on this model has been developed in Yokohama. This system not only benefits clinical performance, but will also add significantly to research on autism.

5.11. Lavie, T., Sturmey, P. "Training staff to conduct a paired-stimulus preference assessment." *J Appl Behav Anal* 2002 Summer;35(2):209-11.

Queens College, Flushing, New York 11367, USA.

Three staff members were trained to conduct stimulus preference assessments using a paired-stimulus format with 8 children with autism. Staff were trained to mastery level using brief instruction, a video model, and rehearsal with verbal feedback. Training took about 80 min per staff member. Results demonstrated that staff rapidly learned to correctly perform paired-stimulus preference assessments with children.

5.12. Grindle, C.F., Remington, B. "Discrete-trial training for autistic children when reward is delayed: a comparison of conditioned cue value and response marking." *J Appl Behav Anal* 2002 Summer;35(2):187-90.

University of Southampton, United Kingdom.

Three children with autism were taught to identify pictures of objects. Their speed of acquisition of receptive speech skills was compared across two conditions. In the cue-value condition, a compound audiovisual stimulus was presented after correct responses and again when a primary reinforcer was delivered after a 5-s delay; in the response-marking condition, a second stimulus was presented after both correct and incorrect responses, but not prior to the primary reinforcer. In both conditions primary reinforcement was

delayed for 5 s. Although the children learned receptive speech skills in both conditions, acquisition was faster in the cue-value condition.

5.13. Kok, A.J., Kong, T.Y., Bernard-Opitz, V. "A comparison of the effects of structured play and facilitated play approaches on preschoolers with autism. A case study." *Autism* 2002 Jun;6(2):181-96. Publication Types: Clinical Trial.

National University of Singapore, Singapore.

This study compared the effect of structured play (SP) and facilitated play (FP) in promoting spontaneity and responsiveness in communication and play behaviors in children with autism. SP is characterized by the use of mass practice trials under the instruction of the experimenter while FP incorporated incidental teaching with multiple exemplars. Eight preschoolers participated in a crossover design of both play conditions. Gains in appropriate communication and play were observed across both treatments. Respondent communicative acts occurred more frequently across all participants during SP compared with FP. The preliminary results indicate an interaction between the mental age of the child and the teaching paradigm used. The need to match treatment goals and specific methods of the play intervention to the skill profile of participants is discussed.

5.14. Sherratt, D. "Developing pretend play in children with autism: a case study." *Autism* 2002 Jun;6(2):169-79.

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A classroom-based intervention study aimed to explore whether it was possible to teach children with autism and additional learning difficulties to use symbolic pretend play. Five children with autism were involved in a 4 month intervention that used structure, affect and repetition. The intervention progressively faded out the structuring over three phases. All the children were able to use some symbolic acts within play. The study suggests that some of the symbolic play was not the result of replicating previously modelled examples but was spontaneous and novel.

5.15. Perez-Gonzalez, L.A., Williams, G. "Multicomponent procedure to teach conditional discriminations to children with autism." *Am J Ment Retard* 2002 Jul;107(4):293-301.

University of Oviedo, Spain. laperez@sci.cpd.uniovi.es

Five children with autism with a history of failing to acquire conditional discriminations learned to discriminate objects in response to spoken names or to match amounts to numbers with a combined blocking procedure. The procedure for teaching object discriminations involved (a) presenting the same spoken word until 10 consecutive correct responses occurred and (b) keeping the left-right location of the objects on the table constant. After mastery, the requirement for changing the spoken word was gradually reduced. Finally, the spoken words were presented randomly. In the final stage, the objects were located randomly. The procedure to teach number matching was similar. All children learned these discriminations with few errors. This procedure may be

beneficial in teaching conditional discriminations to children with learning difficulties.

5.16. Escalona, A., Field, T., Nadel, J., Lundy, B. "Brief report: imitation effects on children with autism." *J Autism Dev Disord* 2002 Apr;32(2):141-4.

University of Miami School of Medicine, Touch Research Institutes, Florida 33101, USA.

Twenty children with autism (mean age, 5 years) were recruited for the study from a school for children with autism. The children were randomly assigned to an imitation (n = 10) or contingently responsive (n = 10) interaction group based on a stratification table for gender and developmental and chronological age. The sessions consisted of four phases, with each phase lasting 3 minutes. In the first phase, the child walked into a room that was furnished with a sofa, a table, chairs, and two sets of identical toys. An adult was in the room sitting very still like a statue (first still-face condition). In the second phase, the adult either imitated the child or was contingently responsive to the child. In the third phase, the adult sat still again (second still-face condition), and in the fourth phase, the adult engaged in a spontaneous interaction. During the third phase (the second still-face condition), the children in the imitation group spent less time in gross motor activity and more time touching the adult, as if attempting to initiate an interaction. The contingency condition appeared to be a more effective way to facilitate a distal social behavior (attention), whereas the imitative condition was a more effective way to facilitate a proximal social behavior (touching).

5.17. Parsons, S., Mitchell, P. "The potential of virtual reality in social skills training for people with autistic spectrum disorders." *J Intellect Disabil Res* 2002 Jun;46(Pt 5):430-43. Publication Types: Review Review, Tutorial

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BACKGROUND: People with autism experience profound and pervasive difficulties in the social domain. Attempts to teach social behaviours tend to adopt either a behavioural or a 'theory of mind' (ToM) approach. The beneficial aspects and limitations of both paradigms are summarized before an examination of how virtual reality technology may offer a way to combine the strengths from both approaches. **METHODS:** This is not an exhaustive review of the literature; rather, the papers are chosen as representative of the current understanding within each broad topic. Web of Science ISI, EMBASE and PsycInfo were searched for relevant articles. **RESULTS:** Behavioural and ToM approaches to social skills training achieve some success in improving specific skills or understanding. However, the failure to generalize learned behaviours to novel environments, and the unwieldy nature of some behavioural methodologies, means that there is a need for a training package that is easy to administer and successful in promoting learning across contexts. **CONCLUSIONS:** Virtual reality technology may be an ideal tool for allowing participants to practise behaviours in role-play situations,

whilst also providing a safe environment for rule learning and repetition of tasks. Role-play within virtual environments could promote the mental simulation of social events, potentially allowing a greater insight into minds. Practice of behaviours, both within and across contexts, could also encourage a more flexible approach to social problem solving. Virtual environments offer a new and exciting perspective on social skills training for people with autistic spectrum disorders.

5.18. Panerai, S., Ferrante, L., Zingale, M. "Benefits of the Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) programme as compared with a non-specific approach." *J Intellect Disabil Res* 2002 May;46(Pt 4):318-27.

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BACKGROUND: Two educational treatments were compared, the Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) programme and the integration programme for individuals with disabilities. **METHODS:** Two groups of eight subjects were matched by gender, chronological and mental age, and nosographic diagnosis (i.e. autism associated with severe intellectual disability, DSM-IV criteria and Childhood Autism Rating Scale scored. The TEACCH programme was applied to the experimental group, while the control group was integrated in regular schools with a support teacher. The Psycho-Educational Profile-Revised and the Vineland Adaptive Behaviour Scale were administered twice with a one-year interval between assessments. **RESULTS:** The scores of the experimental group increased more than the control group scores. Statistically significant differences were obtained in both groups because of the differences in the two approaches.

5.19. Ferguson, A.P., McKinlay, I.A., Hunt, A. "Care of adolescents with severe learning disability from tuberous sclerosis." *Dev Med Child Neurol* 2002 Apr;44(4):256-62.

Central Manchester Primary Care Trust, Newton Heath Health Centre, UK.

A postal study was completed by 138 members of the Tuberous Sclerosis Association for individuals with severe learning disabilities from tuberous sclerosis complex (TSC) (78 males, median 20 years of age; 60 females median 19 years 6 months of age) to investigate the abilities and care needs of these adolescents and young adults. Results were compared with a Salford community survey of young people with severe learning disability (SLD) from a variety of causes (42 males, median 17 years; 29 females, median 17 years 8 months of age). Those with SLD associated with TSC had a higher level of verbal disability and were more dependent for managing toileting and bathing. The young people with TSC were less able to interact socially, showing autistic behaviour. Sexually, they were less aware and less active. Only 20 were thought by their parents to have received sex education.

5.20. Lattimore, L.P., Parsons, M.B., Reid, D.H. "A prework assessment of task preferences among adults with autism beginning a supported job." *J Appl Behav Anal* 2002 Spring;35(1):85-8. Publication Types: Evaluation Studies.

Western Carolina Center, USA.

A prework paired-task assessment was evaluated for identifying work preferences among 3 adults with autism beginning a supported job. When the workers began the job, choices were provided between more and less preferred tasks (determined by previous assessment). Results supported the assessment for identifying single task preferences, but did not reveal preferences of 2 workers for alternate tasks. Results are discussed in terms of evaluating other prework assessments that may reveal task-alternation preferences.

5.21. Shabani, D.B., Katz, R.C., Wilder, D.A., Beauchamp, K., Taylor, C.R., Fischer, K.J. "Increasing social initiations in children with autism: effects of a tactile prompt." *J Appl Behav Anal* 2002 Spring;35(1):79-83. Publication Types: Clinical Trial.

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An ABAB design was used to assess the effects of a tactile prompting device (i.e., a vibrating pager) as a prompt for the social initiations of 3 children with autism during free-play activities with typically developing peers. Results indicated that the tactile prompt was effective in increasing verbal initiations for all 3 children, and responses to peers' initiations were higher for 2 participants when the tactile prompt was used. Efforts to reduce the frequency of prompts while still maintaining rates of initiations were partially successful for 1 participant.

5.22. Williams, C., Wright, B., Callaghan, G., Coughlan, B. "Do children with autism learn to read more readily by computer assisted instruction or traditional book methods? A pilot study." *Autism* 2002 Mar;6(1):71-91. Publication Types: Clinical Trial, Evaluation Studies, Randomized Controlled Trial.

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The study evaluates the progress of eight children aged 3-5 years with autism attending a specialist teaching unit in their development of reading skills in two conditions: computer instructed learning and book based learning. The authors developed a direct observation schedule to monitor autistic behaviours using computerized techniques. The children were matched by age, severity of autistic symptomatology and number of spoken words. They were initially randomly allocated to the computer or book condition and crossed over at 10 weeks. All of the children spent more time on task in the computer condition than in the book condition. By the end of the study after computer assisted learning, five of the eight children could reliably identify at least three words. It was found that children with autism spent more time on reading material when they accessed it through a computer and were less resistant to its use.

5.23. Salt, J., Shemilt, J., Sellars, V., Boyd, S., Coulson, T., McCool, S. "The Scottish Centre for autism preschool treatment programme. II: The results of a controlled treatment outcome study." *Autism* 2002 Mar;6(1):33-46. Publication Types: Clinical Trial, Evaluation Studies.

Scottish Centre for Autism, Department of Child and Family Psychiatry, Glasgow, UK. jeff_salt@hotmail.com

This article evaluates the effectiveness of a developmentally based early intervention programme. Two groups of children were compared, a treatment group and a no-treatment control group. Standardized assessments were administered before and after the intervention period by an independent clinician. Pre-treatment comparisons revealed that the control group had a significantly higher pre-treatment IQ; but the two groups were comparable for age, mental age, socioeconomic status and number of hours of non-experimental therapy. Results demonstrated that children in the treatment group improved significantly more than those in the control group on measures of joint attention, social interaction, imitation, daily living skills, motor skills and an adaptive behaviour composite. A measure of requesting behaviour fell short of statistical significance. The total stress index reduced for treatment group parents and increased for the control group parents (but not significantly). The results of the study are considered to support the efficacy of this treatment approach.

5.24. Williams, M.A., Moss, S.A., Bradshaw, J.L., Rinehart, N.J. "Random number generation in autism." *J Autism Dev Disord* 2002 Feb;32(1):43-7.

Department of Psychology, Monash University, VIC, Australia. mark.williams@sci.monash.edu.au

This study explored the ability of individuals with autism to generate a unique series of digits. Fourteen low-functioning individuals with autism, 14 intellectually disabled individuals, and 14 postgraduate university students generated a series of pseudo-random digits. Individuals with autism were more likely to repeat previous digits than were either of the control groups. The normal control group, however, was less likely to attempt cycling through all digits before repeating. Accordingly, low-functioning individuals with autism may exhibit a short-fall in response inhibition. This finding supports the executive dysfunction theory of autism.

5.25. Thiemann, K.S., Goldstein, H. "Social stories, written text cues, and video feedback: effects on social communication of children with autism." *J Appl Behav Anal* 2001 Winter; 34(4): 425-46. Publication Types: Clinical Trial.

Florida State University, USA thiemann@ku.edu

This study investigated the effects of written text and pictorial cuing with supplemental video feedback on the social communication of 5 students with autism and social deficits. Two peers without disabilities participated as social partners with each child with autism to form five triads. Treatment was implemented twice per week and consisted of 10 min of systematic instruction using visual stimuli, 10 min of social interaction, and 10 min of self-evaluation using video

feedback. Results showed increases in targeted social communication skills when the treatment was implemented. Some generalized treatment effects were observed across untrained social behaviors, and 1 participant generalized improvements in the quality of reciprocal interactions. These findings support recommendations for using visually cued instruction to guide the social language development of young children with autism as they interact with peers without disabilities.

5.26. Zereher, C., Hunt, P., Schuler, A., Webster, J. "Increasing joint attention, play and language through peer supported play." *Autism* 2001 Dec; 5(4): 374-98.

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The purpose of the present study was to examine the effects of participation in an integrated play group on the joint attention, symbolic play and language behavior of two young boys with autism. Two 6-year-old twin brothers participated in this study, along with three typically developing girls, ages 5, 9 and 11. A multiple baseline design was used with three phases: no intervention, intervention with adult coaching, and intervention without adult coaching. After being trained, the three typically developing children implemented the integrated play group techniques in 30 minute weekly play group sessions for over 16 weeks. Results indicate that participation in the integrated play group produced dramatic increases in shared attention to objects, symbolic play acts, and verbal utterances on the part of the participants with autism. These increases were maintained when adult support was withdrawn. Implications of these findings for inclusion of children with autism are discussed.

5.27. Wong, S.K., Tam, S.F. "Effectiveness of a multimedia programme and therapist-instructed training for children with autism." *Int Rehabil Res* 2001 Dec; 24(4):269-78. Publication Types: Evaluation Studies.

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon.

The present study aimed to evaluate the effectiveness of an interactive multimedia training programme and a conventional therapist-instructed training in improving the learning behaviours of children with autism. A multiple-subject, single case-study time-series research design was adopted in the study. Six children with autism, aged 2 years 4 months to 2 years 10 months, were recruited by convenience sampling. They attended a 12-session training programme on basic concepts (e.g. colours, shapes) that was presented as an interactive multimedia training programme and also as a conventional, therapist-led training programme. The attending behaviours and appropriate responses of the subjects were therapist-instructed training programme generally showed improvement in attending behaviours and response rates; participants attending the multimedia programme also showed improvement in their attending behaviours and response rates. The results support the

hypothesis that both training programmes are effective in improving the attending behaviours and appropriate response of children with autism. The authors suggest that, because children with autism respond differently to different training approaches, customized training programmes should be considered for individual children. The implications of the methodology and the potential impact of the present study on the training of children with autism are discussed.

5.28. Bibby, P., Eikeseth, S., Martin, N.T., Mudford, O.C., Reeves, D. "Progress and outcomes for children with autism receiving parent-managed intensive interventions." *Res Dev Disabil* 2001 Nov-Dec; 22(6): 425-47. Publication Types: Evaluation Studies.

Autism & Developmental Disorders Education Research, London, England, United Kingdom.
Peter J Bibby@compuserve.com

Parent managed behavioral interventions for young children with autism are under-researched. We analyzed data from 66 children served by 25 different carry interventions consultants. After a mean of 31.6 months of intervention IQ scores had not changed (N= 22). Vineland adaptive behavior scores had increased significantly by 8.9 points (N=21). No children aged > 72 months attained normal functioning, i.e., IQ> 85 and unassisted mainstream school placement (N=42). Progress for 60 children across 12 months was found for mental age (5.4 months), adaptive behavior (9.7 months), and language (5.1 months). The interventions did not reproduce results from clinic-based professionally directed programs. The effectiveness of the parent-managed intervention model as it has developed and the adequacy of professional services in that model are discussed.

5.29. Field, T., Field, T., Sanders, C., Nadel, J. "Children with autism display more social behaviors after repeated imitation sessions." *Autism* 2001 Sep; 5(3): 317-23. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Based on earlier studies, an adult's imitations of the behaviors of children with autism lead to increased social behavior in the children. The present study explored the effects of repeated sessions of imitation. Twenty children were recruited from a school for children with autism to attend three sessions during which an adult either imitated all of the children's behaviors or simply played with the child. During the second session the children in the imitation group spent a greater proportion of time showing distal social behaviors toward the adult including: (1) looking; (2) vocalizing; (3) smiling; and (4) engaging in reciprocal play. During the third session, the children in the imitation group spent a greater proportion of time showing proximal social behaviors toward the adult including (1) being close to the adult; (2) sitting next to the adult; and (3) touching the adult. These data suggest the potential usefulness of adult imitative behaviour as an early intervention.

5.30. Tjus, T., Heimann, M., Nelson, K.E. "Interaction patterns between children and their teachers when using a specific multimedia and communication strategy: observations from children with autism and mixed intellectual disabilities." *Autism* 2001 Jun;5(2): 175-87. Publication Types: Evaluation Studies.

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This study reports on observed interaction patterns between 20 children with autism and mixed intellectual disabilities (mean chronological = 11:4 years; language age =4:7 years and their nine teachers working with a specially developed multimedia program aiming to increase literacy skills. An increase in verbal expression was found over time for the total group. Children with autism also showed increased enjoyment and willingness to seek help from their teachers. Teachers for both diagnostic groups of children was subdivided according to language age (high versus low), it appears that those with a low language age showed an increased enjoyment. It is concluded that more detailed studies of the interaction patterns between teachers and children are needed, and these should be related to children's language level as well as to diagnostic group.

5.31. Taubman, M., Brierley, S., Wishner, J., Baker, D., McEachin, J., Leaf, R.B. "The effectiveness of a group discrete trial instructional approach for preschoolers with developmental disabilities." *Res Dev Disabil* 2001 May-Jun;22(3):205-19. Publication Types: Evaluation Studies.

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Group behavioral classroom instruction for children with developmental disabilities has been shown to allow for increased efficiency, approximation to naturalistic arrangements, and enhanced opportunity for interaction, social teaching and observational learning. This study examines the effectiveness of a group instructional extension of one to one discrete trial teaching, which involves the overlapping of trials between students along with the use of sequential and choral group teaching. A multiple baseline design across tasks was employed to examine the effectiveness of the group instructional approach in promoting acquisition of educational skills among preschoolers with autism and other developmental disabilities. A time sample interval assessment of components of the group instruction was also conducted. The approach was demonstrated to consistently increase correct responding across the task areas. Results are discussed in terms of the advantages of the group instructional approach as an adjunct to one to one discrete trial instruction.

5.32. Sarokoff, R.A., Taylor, B.A., Poulson, C.L. "Teaching children with autism to engage in conversational exchanges: script fading with embedded textual stimuli." *J Appl Behav Anal* 2001 Spring;34(1):81-4.

Graduate Center and Queens College, CUNY, USA.

A multiple baseline across three sets of stimuli was used to assess the effects of a script-fading procedure using embedded text to teach 2 children with autism to engage in conversation statements about the stimuli. Both students stated all the scripted statements, and unscripted statements also increased. Generalization was assessed with novel peers and with untrained stimuli.

5.33. Laushey, K.M., Heflin, L.J. "Enhancing social skills of kindergarten children with autism through the training of multiple peers as tutors." *J Autism Dev Disord* 2000 Jun;30(3):183-93.

Georgia State University, Department of Educational Psychology and Special Education, Atlanta 30303-3083, USA.

Many students with autism are being served in inclusive settings. Early intervention programs, traditionally home-based, are beginning to create center-based options which incorporate typically developing peers. One of the arguments for the use of inclusive programs is that students with autism will benefit from their exposure to and interactions with typical peers. Unfortunately, research suggests that in inclusive settings, typical peers and peers with autism do not always interact without prompting from an adult. This study used an ABAB design to determine if a peer buddy approach in which all students were trained to interact in dyads would increase non-adult-directed interactions. Data collected on the students with autism indicate that the peer buddy approach significantly increased their appropriate social interactions. Follow-up data on one of the students indicates generalization of appropriate social interactions to a new classroom.

5.34. Moore, M., Calvert, S. "Brief report: vocabulary acquisition for children with autism: teacher or computer instruction." *J Autism Dev Disord* 2000 Aug;30(4):359-62.

Department of Psychology, Georgetown University, Washington, DC 20057, USA.

This study examined the impact of computers on the vocabulary acquisition of young children with autism. Children's attention, motivation, and learning of words was compared in a behavioral program and an educational software program. The educational software program was designed to parallel the behavioral program, but it added perceptually salient qualities such as interesting sounds and object movement. Children with autism were more attentive, more motivated, and learned more vocabulary in the computer than in the behavioral program. Implications are considered for the development of computer software to teach vocabulary to children who have autism.

5.35. Brodin, J., Jonson, U. "Computer play centres for children with disabilities." *Int J Rehabil Res* 2000 Jun;23(2):125-8.

Department of Human Development, Learning and Special Education, Stockholm Institute of Education, Sweden.

For all children play is the leading and dominating activity in childhood and essential in child development. Many children

with severe disabilities have limited opportunities to play and need support. Computer play can be a good support in habilitation/rehabilitation of children who have not earlier been able to play independently. Eight pilot computer play centres were started in Sweden in 1992 and since then the number of centres has increased. The target group was children with disabilities on the level before reading and writing. This brief report is a description of the computer play centres and the first three activity years.

5.36. Capps, L., Losh, M., Thurber, C. "The frog ate the bug and made his mouth sad": narrative competence in children with autism." *J Abnorm Child Psychol* 2000 Apr;28(2):193-204. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Psychology, University of California, Berkeley 94720-1650, USA.

This study compares the narrative abilities of 13 children with autism, 13 children with developmental delays, and 13 typically developing children matched on language ability. Although groups did not differ in their use of causal language or internal state terms, children with autism and children with developmental delays were less likely than typical children to identify the causes of characters' internal states. Rather, they tended simply to label emotions and explain actions. Children with autism and children with developmental delays also relied on a more restricted range of evaluative devices, which both convey point of view and maintain listener involvement. In addition, the narrative abilities of children with autism were linked to performance on measures of theory of mind and an index of conversational competence, whereas this was not the case among children with developmental delays. Findings are discussed in relation to the social, cognitive, and emotional underpinnings and consequences of narrative activity.

5.37. Jahr, E., Eldevik, S., Eikeseth, S. "Teaching children with autism to initiate and sustain cooperative play." *Res Dev Disabil* 2000 Mar-Apr;21(2):151-69.

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This study investigated the acquisition, transfer, and maintenance of cooperative play in six children with autism. Two approaches were compared. In one approach, the participants observed two models engaging in cooperative play, before taking the place of one of the models while the play episode just observed was repeated. The second approach was identical to the first except that the participants were now required to verbally describe the modeled play episode before taking the place of one of the models. During training, modeled play episodes varied across play topics, and the criterion for mastery was first trial learning of novel play episodes. A nonconcurrent multiple baseline design across participants was applied. The results showed that the participants failed to acquire cooperative play until the verbal description was included in the training procedure. Following training with verbal description, all participants: a) could

initiate episodes and sustain episodes initiated by their play partner; b) were able to take turns in episodes that were considerably longer than the episodes practiced during training; c) varied their play within and between play episodes; and, d) transferred those skills across play partners, settings, and time.

5.38. Schmit, J., Alper, S., Raschke, D., Ryndak, D. "Effects of using a photographic cueing package during routine school transitions with a child who has autism." *Ment Retard* 2000 Apr;38(2):131-7.

Department of Special Education, University of Northern Iowa, Cedar Falls 50614-0601, USA.

Making successful transitions from one activity to another is difficult for many children, particularly those who have cognitive, language, or behavioral disabilities. Appropriately terminating one activity and initiating another in a timely fashion is a skill important for young children to learn prior to entering kindergarten. The efficacy of teaching a young child labeled as having autism to make successful transitions in daily routines in three different school settings through the use of photographic cue package was examined. A multiple baseline across-settings design was used to evaluate the efficacy of the intervention. Implications for the use of photographic cue packages in teaching a variety of activities to young children are discussed.

5.39. Biederman, G.B., Stepaniuk, S., Davey, V.A., Raven, K., Ahn, D. "Observational learning in children with Down syndrome and developmental delays: the effect of presentation speed in videotaped modelling." *Downs Syndr Res Pract* 1999 Aug;6(1):12-8.

Division of Life Sciences, University of Toronto, Scarborough, Ontario, Canada. bieder@scar.utoronto.ca

Children with severe developmental delays (three with Down syndrome and three with autism as the primary diagnosis) observed a videotaped model performing two basic dressing skills without prompting, verbal or otherwise, or explanation by an instructor. In a within-subjects design, dressing skills that were presented at a relatively slow presentation speed through videotaped modelling were eventually performed better than those presented at a relatively fast speed. These data in combination with evidence from this laboratory that passive modelling of basic skills is more effective than interactive modelling (e.g., Biederman, Fairhall, Raven, & Davey, 1998; Biederman, Davey, Ryder, & Franchi, 1994; Biederman, Ryder, Davey, & Gibson, 1991) suggest that standard instructional techniques warrant reexamination both from the basis of instructional effectiveness and the efficient use of the allotment of teacher time.

5.40. Backman, B., Pilebro, C. "Visual pedagogy in dentistry for children with autism." *ASDC J Dent Child* 1999 Sep-Oct;66(5):325-31, 294.

Department of Pedodontics, Faculty of Odontology, Umea University, Sweden.

The aim of the present study is to present and evaluate a model based on visual pedagogy for the introduction of dentistry to preschool children with autism. The model is based on the knowledge that it is easier for these children to communicate via pictures than via words. A book has been produced with distinct color-prints describing every step when visiting the dentist. The project has been designed in cooperation with the multi-professional team involved with the children. A total of sixteen children with autism participated in the project. Evaluation was done after 1.5 years. The ability of the children to cooperate is compared with that of sixteen children with autism of the same ages who were not treated with this method. The capacity of the children in the project to cooperate during dental treatment is superior to that of the control-children. Visual pedagogy is a way of introducing dentistry to children with autism.

5.41. Farrant, A., Blades, M., Boucher, J. "Recall readiness in children with autism." *J Autism Dev Disord* 1999 Oct;29(5):359-66.

Department of Human Communication Sciences, University of Sheffield, United Kingdom.

When people are asked to learn information they need to judge when they have encoded the information accurately and will be able to retrieve it correctly. Making such a judgment is an aspect of metacognitive ability, and is referred to as "recall readiness." Previous researchers have not considered recall readiness in children with autism, therefore we asked matched groups of children with autism, children with mental retardation, and normally developing children (mean mental age: 7 years) to study several pictures of objects until they felt ready to recall all the objects without error. Their recall was then tested. The children with autism and the children with mental retardation had impaired recall readiness compared to the normally developing children. We discuss this result with reference to other research into the metacognitive abilities of children with autism.

5.42. Yamamoto, J., Miya, T. "Acquisition and transfer of sentence construction in autistic students: analysis by computer-based teaching." *Res Dev Disabil* 1999 Sep-Oct;20(5):355-77.

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In this study, we examined the conditions necessary to construct appropriate sentences in three autistic students using computer-based training and testing procedure. In Experiment 1, when a picture was presented on the computer display as a sample stimulus, the student was required to construct an appropriate sentence with five words. After training with three stimuli, each student could construct the correct sentence for 24 untrained stimuli. Appropriate vocal responses also emerged. In Experiment 2, the appropriate use of particles, which specify the subject and the object, was acquired by particle choice or sentence construction training. The rule was transferred to untrained stimuli and writing response. These results are discussed in terms of applicability of computer-based training for establishing appropriate sequential responding and particle usage in autistic students.

5.43. Buitelaar, J.K., van der Wees, M., Swaab-Barneveld, H., van der Gaag, R.J. "Verbal memory and Performance IQ predict theory of mind and emotion recognition ability in children with autistic spectrum disorders and in psychiatric control children." *J Child Psychol Psychiatry* 1999 Sep;40(6):869-81.

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This study was designed to examine the developmental and cognitive correlates of theory of mind (ToM) and emotion recognition ability in children with autism (N = 20), with pervasive developmental disorder-not otherwise specified (PDD-NOS) (N = 20), and in psychiatric control children (N = 20). The diagnostic groups were person-to-person matched on age and verbal IQ. The age of the children was between 8 and 18 years; their Full Scale IQ was at least 65. The test battery included tasks for the matching and the context recognition of emotional expressions, and a set of first- and second-order ToM tasks. The relationships between composite domain scores and the subjects' age, Verbal IQ, Performance IQ, verbal memory, visual memory, and gender were examined in bivariate and multivariate analyses. Further, the subjects who reliably and consistently passed the tasks of a domain and those who could not were compared on developmental and cognitive characteristics. Overall, the results of the various analyses converged and indicated that verbal memory, Performance IQ, age and gender were the best predictors of social cognitive ability.

5.44. Kasari, C., Freeman, S.F., Bauminger, N., Alkin, M.C. "Parental perspectives on inclusion: effects of autism and Down syndrome." *J Autism Dev Disord* 1999 Aug;29(4):297-305.

Graduate School of Education and Information Studies, University of California, Los Angeles, USA.

This study examined the effects of the child's diagnosis (autism vs. Down syndrome), age, and current educational placement on parental perceptions toward inclusion for their child with disabilities. Parents of children with autism and with Down syndrome completed surveys regarding their opinions on their child's current educational placement, their desire for changing the current placement, and their views on inclusive education. Results indicated that diagnosis, age, and current placement influenced parental opinion on the ideal educational placement for their child. Parents of children with Down syndrome were significantly more likely to endorse inclusion (full-time placement in general education) as the ideal educational program for their child whereas parents of children with autism were more likely to endorse mainstreaming (consistent part-time placement with general education students). Parents of younger children and parents whose children were already placed in general education programs were more positive towards inclusion than parents of older children or students currently in special education. Findings are discussed in terms of child characteristics and prevailing educational practices.

5.45. Mottron, L., Belleville, S., Menard, E. "Local bias in autistic subjects as evidenced by graphic tasks: perceptual hierarchization or working memory deficit?" *J Child Psychol Psychiatry* 1999 Jul;40(5):743-55.

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In the present study, copying tasks were used to assess hierarchical aspects of visual perception in a group of 10 nonsavant autistic individuals with normal intelligence. In Experiment 1, the hierarchical order of graphic construction and the constancy of this order were measured for the copying of objects and nonobjects. In comparison to control participants, autistic individuals produced more local features at the start of the copying. However, they did not differ from controls with respect to graphic constancy. Experiment 2 measured the effect of geometrical impossibility on the copying of figures. Results revealed that autistic individuals were less affected by figure impossibility than were controls. Therefore, these experiments seem to support the notion of a local bias for visual information processing in individuals with autism. Two interpretations are proposed to account for this effect. According to the hierarchical deficit hypothesis, individuals with autism do not manifest the normal global bias in perceiving scenes and objects. Alternatively, the executive function hypothesis suggests that autism brings about limitations in the complexity of information that can be manipulated in short-term visual memory during graphic planning.

5.46. Plaisted, K., Swettenham, J., Rees, L. "Children with autism show local precedence in a divided attention task and global precedence in a selective attention task." *J Child Psychol Psychiatry* 1999 Jul;40(5):733-42.

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Children with a diagnosis of autism and typically developing children were given two variations of the Navon task (Navon, 1977), which required responding to a target that could appear at the global level, the local level, or both levels. In one variation, the divided attention task, no information was given to children regarding the level at which a target would appear on any one trial. In the other, the selective attention task, children were instructed to attend to either the local or the global level. Typically developing children made most errors when the target appeared at the local level whereas children with autism made more errors when the target appeared at the global level in the divided attention task. Both groups of children were quicker to respond to the global target than the local target in the selective attention task. The presence of normal global processing in the children with autism in one task but not in the other is discussed in terms of a deficit in mechanisms that inhibit local information in the absence of overt priming or voluntary selective attention to local information.

5.47. Taylor, B.A., Levin, L. "Teaching a student with autism to make verbal initiations: effects of a tactile prompt." *J Appl Behav Anal* 1998 Winter;31(4):651-4.

Alpine Learning Group, Paramus, New Jersey 07652, USA.

This study examined the effects of a tactile prompting device (the Gentle Reminder) as a prompt for a student with autism to make verbal initiations about his play activities. A multiphase multielement design was used to assess the effects of the device in prompting initiations toward an adult in three different play contexts. Follow-up probes were conducted during cooperative learning activities with typically developing peers in the student's regular education class. The results suggest that the device serves as an effective, unobtrusive prompt for verbal initiations during play contexts and during cooperative learning activities.

DIAGNOSIS

6.1. Hardan, A.Y., Kilpatrick, M., Keshavan, M.S., Minshew, N.J. "Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism." *J Child Neurol.* 2003 May;18(5):317-24.

Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA.

This study was conducted to examine the volume of the basal ganglia in individuals with autism and to evaluate whether performance on specific motor tasks correlated with the volume of these structures. Volumetric measurements of the caudate nucleus and putamen were obtained from magnetic resonance images (MRI) of 40 non-mentally retarded individuals with autism and 41 healthy controls. Motor performance was assessed in these subjects by using the Finger Tapping Test, the Grooved Pegboard Test, and the measurement of Grip Strength. No volumetric differences of the basal ganglia were found between the two groups after adjusting for brain volume. The autistic subjects' performance was slower on the Grooved Pegboard Test and weaker on Grip Strength. Our findings suggest that the motor deficits observed in autism may not be related to structural abnormalities of the basal ganglia, and other brain regions, such as the cerebellum and the frontal lobe, may be involved in the pathophysiology of motor disturbances in autism.

6.2. Tadevosyan-Leyfer, O., Dowd, M., Mankoski, R., Winklosky, B., Putnam, S., McGrath, L., Tager-Flusberg, H., Folstein, S.E. "A principal components analysis of the Autism Diagnostic Interview-Revised." *J Am Acad Child Adolesc Psychiatry.* 2003 Jul;42(7):864-72. Publication Types: Validation Studies.

Department of Psychiatry, Tufts New England Medical Center, Boston, MA, USA.

OBJECTIVE: To develop factors based on the Autism Diagnostic Interview-Revised (ADI-R) that index separate components of the autism phenotype that are genetically relevant and validated against standard measures of the constructs. **METHOD:** ADIs and ADI-Rs of 292 individuals with autism were subjected to a principal components analysis using VARCLUS. The resulting variable clusters were validated against standard measures. **RESULTS:** Six clusters of variables emerged: spoken language, social intent, compulsions, developmental milestones, savant skills and sensory aversions. Five of the factors were significantly correlated with the validating measures and had good internal consistency, face validity, and discriminant and construct validity. Most intraclass correlations between siblings were adequate for use in genetic studies. **CONCLUSION:** The ADI-R contains correlated clusters of variables that are valid, genetically relevant, and that can be used in a variety of studies.

6.3. Newson, E., Le Marechal, K., David, C. "Pathological demand avoidance syndrome: a necessary distinction within the pervasive developmental disorders." *Arch Dis Child.* 2003 Jul;88(7):595-600. Publication Types: Review, Review, Tutorial.

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A proposal is made to recognise pathological demand avoidance syndrome (PDA) as a separate entity within the pervasive developmental disorders, instead of being classed under "pervasive developmental disorder not otherwise specified" (PDDnos, DSM-IV). Discriminant functions analysis shows PDA to be significantly different on many counts from classic autism and Asperger's syndrome, both separately and together, including an equal sex ratio (150 cases). Demand avoidance using social manipulation is seen in all children, which strongly contrasts with the features of autistic spectrum disorders. A criterial structure is described, supported by statistical data from a random sample of 50 children diagnosed with PDA, together with a follow up sample of 18 young adults.

6.4. Carney, R.M., Wolpert, C.M., Ravan, S.A., Shahbazian, M., Ashley-Koch, A., Cuccaro, M.L., Vance, J.M., Pericak-Vance, M.A. "Identification of MeCP2 mutations in a series of females with autistic disorder." *Pediatr Neurol.* 2003 Mar;28(3):205-11.

Department of Medicine and the Center for Human Genetics, Duke University Medical Center, Durham, North Carolina 27710, USA.

Rett disorder and autistic disorder are both pervasive developmental disorders. Recent studies indicate that at least 80% of Rett Disorder cases are caused by mutations in the methyl-CpG-binding protein 2 (MeCP2) gene. Since there is some phenotypic overlap between autistic disorder and Rett disorder, we analyzed 69 females clinically diagnosed with autistic disorder for the presence of mutations in the MeCP2 gene. Two autistic disorder females were found to have de novo mutations in the MeCP2 gene. These data provide additional evidence of variable expression in the Rett disorder phenotype and suggest MeCP2 testing may be warranted for females presenting with autistic disorder.

6.5. Cohen, I.L. "Criterion-related validity of the PDD Behavior Inventory." *J Autism Dev Disord.* 2003 Feb;33(1):47-53.

Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA.

The PDD Behavior Inventory (PDDBI) is a rating scale filled out by parents and teachers that is designed to assess response to intervention in children with PDD. It consists of subscales that measure both maladaptive and adaptive behaviors and also provides a summary "Autism Score" reflective of the severity of the condition. The scale has been shown to have very good internal consistency as well as developmental and construct validity. In this study, the PDDBI's criterion-related validity was assessed. Correlations with the Childhood Autism Rating Scale and the Autism Diagnostic Interview-Revised were good. Selected maladaptive scales from the PDDBI correlated well with comparable factors of the

Nisonger Child Behavior Rating Form. The adaptive sections of the PDDBI correlated highly with the Griffiths Mental Development Scales and with the Vineland Adaptive Behavior Scales. These results confirm the validity of the PDDBI and suggest that the scale will have value in assessing treatment-related changes in maladaptive and adaptive behaviors associated with PDD.

6.6. Cohen, I.L., Schmidt-Lackner, S., Romanczyk, R., Sudhalter, V. "The PDD Behavior Inventory: a rating scale for assessing response to intervention in children with pervasive developmental disorder." *J Autism Dev Disord.* 2003 Feb;33(1):31-45. Publication Types: Validation Studies.

Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY 10314, USA.

The PDD Behavior Inventory (PDDBI) is a rating scale filled out by caregivers or teachers that was designed to assess children having a Pervasive Developmental Disorder (PDD; autism, Asperger disorder, PDD-NOS, or childhood disintegrative disorder). Both adaptive and maladaptive behaviors are assessed in the scale, making it useful for treatment studies in which decreases in maladaptive behaviors and improvements in adaptive social and language skills relevant to PDD are expected. The adaptive behaviors assessed include core features of the disorder such as joint attention skills, pretend play, and referential gesture. The maladaptive behaviors sample a wide variety of behaviors observed in both lower- and higher-functioning individuals and include stereotyped behaviors, fears, aggression, social interaction deficits, and aberrant language. The inventory was found to have a high degree of internal consistency. Interrater reliability was better for adaptive behaviors than for maladaptive behaviors. Factor analyses confirmed the structure of the PDDBI and indicated good construct validity. In a subsample of children between 3 and 6 years of age, raw scores for adaptive behaviors increased with age in the parent and teacher versions, as did measures of social pragmatic problems. It was concluded that the PDDBI is both reliable and valid and is useful in providing information not typically available in most instruments used to assess children with PDD.

6.7. Tsatsanis, K.D., Dartnall, N., Cicchetti, D., Sparrow, S.S., Klin, A., Volkmar, F.R. "Concurrent validity and classification accuracy of the Leiter and Leiter-R in low-functioning children with autism." *J Autism Dev Disord.* 2003 Feb;33(1):23-30. Publication Types: Validation Studies.

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The concurrent validity of the Leiter International Performance Scale (Leiter) and Leiter International Performance Scale-Revised (Leiter-R) was examined in a sample of children with autism who could not be assessed with more traditional measures of intelligence (e.g., the Wechsler scales). The sample consisted of 26 children ranging in age from 4 to 16 years.

The correlation between the Leiter scales was high ($r = .87$), and there was a difference of 3.7 points between the two mean scores, nonsignificant at both statistical and clinical levels. However, significant intraindividual discrepancies were present in 10 cases, 2 of which were both large (24 and 36 points) and clinically meaningful. The mean profile of performance on Leiter-R subtests is also presented for this sample of children with autism, to allow for comparison with other groups. Based on the results of this initial evaluation, together with the current normative data, good psychometric properties, and availability of global and subtest scores with the Leiter-R, the instrument is generally recommended for use with children with autism. However, because of changes in the design of the Leiter-R, there may be greater clinical success with the original Leiter for those children who are very low functioning and severely affected, particularly younger children.

6.8. Howlin, P. "Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and Asperger syndrome." *J Autism Dev Disord.* 2003 Feb;33(1):3-13. Publication Types: Review, Review, Academic.

Department of Psychology, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK.
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The question of whether Asperger syndrome and high-functioning autism should be considered as the same or different conditions has been a source of debate and controversy over recent years. In the present study, 34 adults with autism who had shown early delays in language were compared with 42 individuals who were reported to have had no such delays, either in their use of words or phrases. All participants were at least 18 years of age, had a nonverbal IQ of 70 or above and met ADI-R criteria for age of onset, communication and social impairments, and stereotyped behaviors. Those in the language delay group were diagnosed as having high-functioning autism. The remainder were designated as having Asperger syndrome. The groups were matched for age, nonverbal IQ and gender. No significant differences were found between the groups either in their total ADI-R algorithm scores, or in their algorithm scores on individual domains. Social outcome ratings and ADI-R scores based on current functioning also failed to differentiate between the groups. Scores on tests of language comprehension and expression were also similar, but in both groups language abilities were well below chronological age level. The implications of these results with respect to the differences between Asperger syndrome and high-functioning autism are discussed. The poor performance on language tests also challenges the assumption that early language development in Asperger syndrome is essentially normal.

6.9. Oliver, C.J. "Triage of the autistic spectrum child utilizing the congruence of case management concepts and Orem's Nursing Theories." *Lippincott's Case Manag.* 2003 Mar-Apr;8(2):66-82. cjo@interaccess.com

The purpose of this project was to design and implement a case management framework for the benefit of children diagnosed with an autistic spectrum disorder (ASD). The process consisted of selecting two children exhibiting symptoms of an ASD and managing them across a continuum of care. Methodological structure was derived from case management standards of practice and Orem's Nursing Theories. Although some objectives sustained a slight delay because of variances, findings revealed successful outcomes based on progression toward measurable case management goals. The children were directed to appropriate school placements and habilitative therapies in an efficient manner. Their parents received support and education related to special needs children. The process yielded assurance that Orem's Nursing Theories and case management concepts articulate seamlessly within nursing care boundaries.

6.10. Kurita, H., Osada, H., Shimizu, K., Tachimori, H. "Validity of DQ as an estimate of IQ in children with autistic disorder." *Psychiatry Clin Neurosci*. 2003 Apr;57(2):231-3.

Department of Mental Health, Graduate School of Medicine, University of Tokyo, Japan. hkurita@m.u-tokyo.ac.jp

The purpose of the present paper was to test the validity of developmental quotients (DQ) on the Mental Development Scale for Infants and Young Children (MDSIYC) as an estimate of intelligence quotient (IQ). Correlations were carried out of its DQ with an IQ on the Japanese version of the Stanford-Binet in 94 children with Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV) autistic disorder. With IQ, DQ in the five MDSIYC areas (motor, play, socialization, self-help, and speech) and full-scale DQ (mean of five-area DQ) had significant correlations (Pearson r) of 0.46, 0.56, 0.53, 0.46, 0.85, and 0.68, respectively, suggesting that speech DQ is the most valid estimate of IQ.

6.11. Ogai, M., Matsumoto, H., Suzuki, K., Ozawa, F., Fukuda, R., Uchiyama, I., Suckling, J., Isoda, H., Mori, N., Takei, N. "fMRI study of recognition of facial expressions in high-functioning autistic patients." *Neuroreport*. 2003 Mar 24;14(4):559-63.

Department of Psychiatry and Neurology, University school of medicine, 20-1, Handayama 1-chome, Hamamatsu 431-3192, Japan.

Autistic disorder is associated with deficits in social function. The disorder may be related to dysfunction in the brain regions that are involved in the process of recognizing facial expressions of other persons. Using fMRI, we investigated whether autistic patients with relatively high IQ would have different brain activation on the tasks of recognition of facial expressions (i.e. faces expressing disgust, fear, and happiness) compared with normal control subjects. In disgust and fear recognition tasks, there were different patterns of brain activation in the cortico-limbic neural circuits between autistic and normal groups. Patients with autistic disorder may have difficulty in grasping facially expressed emotions

in others, and thereby cannot manipulate the interpersonally derived information.

6.12. Gauthier, J., Joobee, R., Mottron, L., Laurent, S., Fuchs, M., De Kimpe, V., Rouleau, G.A. "Mutation screening of FOXP2 in individuals diagnosed with autistic disorder." *Am J Med Genet*. 2003 Apr 15;118A(2):172-5.

Research Institute of the McGill University Health Center, 1650 Cedar Ave, Montreal, Canada.

Although it is well established that genetic factors play an important role in the etiology of autistic disorder (AD), no specific genes have as yet been implicated. Genetic epidemiological data, particularly the sharp fall in concordance rates from monozygotic to dizygotic twins, indicate that the mode of transmission of this disorder is complex and may involve several genes. The 7q31 locus has been repeatedly linked to AD, suggesting that this chromosomal region is likely to harbor a susceptibility gene for AD. Recently, variations in the FOXP2 gene were reported to be responsible for a severe speech and language disorder. Because of the chromosomal location of FOXP2 (7q31) and the putative implication of the 7q31 region both in autistic and in language disorders (a feature of AD), it has been hypothesized that FOXP2 may be implicated in the pathophysiology of AD. To test this hypothesis, we screened the FOXP2 gene coding sequence for mutations in subjects diagnosed with AD and in normal controls. We identified four silent polymorphisms that were equally distributed between patients and controls. Using an intra-family association design, we identified no transmission disequilibrium in any of the four identified alleles, suggesting that the FOXP2 gene does not play a significant role in AD. Copyright 2003 Wiley-Liss, Inc.

6.13. Greicius, M.D. "Neuroimaging in developmental disorders." *Curr Opin Neurol*. 2003 Apr;16(2):143-6. Publication Types: Review, Review, Tutorial.

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PURPOSE OF REVIEW: This review considers the role of neuroimaging in developmental disorders by highlighting recent studies in two distinct, but overlapping, developmental disorders: autism and fragile X syndrome. **RECENT FINDINGS:** After a decade of conflicting results in neuroimaging studies of autism, recent studies have provided some convergent data. One well-replicated finding is that autistic subjects have larger brains. Further, this enlargement, present as early as 3 years of age, appears to represent accelerated growth in infancy and may be followed by slowed growth in late childhood. Other findings are discussed but considered preliminary in the absence of converging evidence or replication studies. Recent work in fragile X syndrome suggests aberrant fronto-striatal and fronto-parietal networks and relates these abnormalities "forward" to behavior and "backward" to decreased protein expression. **SUMMARY:** As

the field of neuroimaging has matured, it has revealed its promise as a safe, reliable, in-vivo tool in the study of developmental disorders. By insisting on larger, more homogeneous patient groups and longitudinal rather than cross-sectional studies, the field is poised to fulfill its ultimate role of linking defects in molecular biology to aberrant behavior.

6.14. Stone, W.L., Coonrod, E.E., Pozdol, S.L., Turner, L.M. "The Parent Interview for Autism-Clinical Version (PIA-CV): a measure of behavioral change for young children with autism." *Autism*. 2003 Mar;7(1):9-30. Publication Types: Evaluation Studies.

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The Parent Interview for Autism-Clinical Version (PIA-CV) was developed to measure autism symptom severity across a wide range of behavioral domains. Two studies were conducted to examine the psychometric properties of the PIA-CV for a sample of children under 3 years old. Results of study 1 revealed adequate internal consistency for nine of the 11 PIA-CV dimensions, as well as significant group differences on social-communication domains between 2-year-old children with autism and a developmentally matched sample. Study 2 examined the association between changes in PIA-CV scores and changes in autism symptomatology from age 2 to age 4. Results revealed that changes on PIA-CV dimensions assessing social and communication skills were associated with clinically significant behavioral and diagnostic improvements. These findings support the utility of the PIA-CV for obtaining ecologically valid information from parents and for measuring behavioral change in young children with autism.

6.15. Jansen, L.M., Gispens-de Wied, C.C., van der Gaag, R.J., van Engeland, H. "Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress." *Neuropsychopharmacology*. 2003 Mar;28(3):582-90.

UMC Utrecht, Department of Child and Adolescent Psychiatry, HP F05.126, PO Box 85500, 3508 GA Utrecht, The Netherlands. L.M.C.Nauta-Jansen@psych.azu.nl

Multiple Complex Developmental Disorder (MCDD) represents a distinct group within the autistic spectrum based on symptomatology. Unlike autistic children, part of MCDD children develop schizophrenia in adult life. Despite the differences, patients of both disorders are mainly characterized by abnormal reactions to their social environment. At the biological level, we showed in a previous study that MCDD children have a reduced cortisol response to psychosocial stress. Given the fact that autistic children clinically show more social impairments, it was hypothesized that they may have even further decreased cortisol responses to psychosocial stress than MCDD patients. Therefore, 10 autistic children were compared to 10 MCDD children and 12 healthy control children in their response to a psychosocial

stressor, consisting of a public speaking task. In order to test whether any impairments in the biological stress response are specific for psychosocial stress, the autistic children were compared with 11 MCDD children and 15 control children in their response to a physical stressor, consisting of 10 min of bicycle exercise. Heart rate and salivary cortisol levels were used as indicators of response to the stress tests. Autistic children showed a relatively elevated cortisol response to psychosocial stress, in contrast to MCDD children who showed a reduced cortisol response. No differences in heart rate or cortisol responses to the physical stress test were found. The specific difference between autistic and MCDD children in their cortisol response to psychosocial stress indicates that the disturbed reactions to the social environment observed in these disorders may have different biological backgrounds.

6.16. Vourc'h, P., Martin, I., Marouillat, S., Adrien, J.L., Barthelemy, C., Moraine, C., Muh, J.P., Andres, C. "Molecular analysis of the oligodendrocyte myelin glycoprotein gene in autistic disorder." *Neurosci Lett*. 2003 Feb 27;338(2):115-8.

Genetique de la Deficience Mentale et de l'Autisme, INSERM U 316, Faculte de Medecine, 2bis, Boulevard Tonnelles, 37032, Tours Cedex, France.

We previously observed in four autistic patients a new allele (GXAlu 5) of the GXAlu microsatellite marker located in intron 27b of the neurofibromatosis type 1 (NF1) gene (17q11.2). This large intron contains the OMGP gene, coding for the oligodendrocyte myelin glycoprotein expressed by neurons and oligodendrocytes. In the present work, we analysed the distribution of a coding single nucleotide polymorphism (OMGP62) of the OMGP gene, the nearest gene to the GXAlu marker, in a control population (n=101) and in an autistic group (n=65). We observed no significant difference in allele distribution comparing these two groups ($\chi^2=1.81$; $P=0.179$). When distinguishing an autistic group with a developmental quotient (DQ) higher than 30 (n=37) and one with a DQ lower than 30 (n=28), we observed an association between allele A and the group with the highest DQ ($P=0.015$). We found no other polymorphism using SSCP screening and DNA sequencing in the OMGP coding region in 16 autistic patients bearing OMGP62 allele A.

6.17. Allen, G., Courchesne, E. "Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism." *Am J Psychiatry*. 2003 Feb;160(2):262-73.

Laboratory for Research on the Neuroscience of Autism, San Diego Children's Hospital Research Center, La Jolla, CA 92037, USA.

OBJECTIVE: Recent years have seen a revolution in views regarding cerebellar function. New findings suggest that the cerebellum plays a role in multiple functional domains: cognitive, affective, and sensory as well as motor. These findings imply that developmental cerebellar pathology could play a role in certain nonmotor functional deficits, thereby

calling for a broader investigation of the functional consequences of cerebellar pathology. Autism provides a useful model, since over 90% of autistic cerebella examined at autopsy have shown well-defined cerebellar anatomic abnormalities. The aim of the present study was to examine how such pathology ultimately impacts cognitive and motor function within the cerebellum. **METHOD:** Patterns of functional magnetic resonance imaging (fMRI) activation within anatomically defined cerebellar regions of interest were examined in eight autistic patients (ages 14-38 years) and eight matched healthy comparison subjects performing motor and attention tasks. For the motor task, subjects pressed a button at a comfortable pace, and activation was compared with a rest condition. For the attention task, visual stimuli were presented one at a time at fixation, and subjects pressed a button to every target. Activation was compared with passive visual stimulation. **RESULTS:** While performing these tasks, autistic individuals showed significantly greater cerebellar motor activation and significantly less cerebellar attention activation. **CONCLUSIONS:** These findings shed new light on the cerebellar role in attention deficits in autism and suggest that developmental cerebellar abnormality has differential functional implications for cognitive and motor systems.

6.18. Tsatsanis, K.D. "Outcome research in Asperger syndrome and autism." *Child Adolesc Psychiatr Clin N Am.* 2003 Jan;12(1):47-63, vi.

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This article presents findings from the outcome literature on autism, Asperger syndrome (AS), and related disorders. The discussion of outcome principally focuses on life adaptation, but also considers outcome in AS in relationship to other diagnostic groups and across time. The current research in this area is neither substantial nor systematic. Thus, in this examination of the literature, the goal is to highlight salient findings, but also to put forward questions that might direct meaningful research in this area for the future and to consider implications for treatment.

6.19. Klin, A., Volkmar, F.R. "Asperger syndrome: diagnosis and external validity." *Child Adolesc Psychiatr Clin N Am.* 2003 Jan;12(1):1-13, v. Publication Types: Review, Review, Tutorial.

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This article provides an overview of the history and clinical features of Asperger syndrome and considers guidelines for clinical assessment and treatment. A review of issues related to external validity is provided that points out the limitations of current research and lists several potentially beneficial areas of investigation into the nosologic status of the condition. It concludes with a discussion of the unequivocal need of individuals with severe social disabilities for comprehensive and adequate educational services and other treatments,

regardless of the fact that the validity and usefulness of this specific diagnostic concept is far from resolved.

6.20. Stefanatos, G.A., Kinsbourne, M., Wasserstein, J. "Acquired epileptiform aphasia: a dimensional view of Landau-Kieffner syndrome and the relation to regressive autistic spectrum disorders." *Neuropsychol Dev Cogn Sect C Child Neuropsychol.* 2002 Sep;8(3):195-228. Publication Types: Review, Review, Academic.

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Acquired epileptiform aphasia (AEA) is characterized by deterioration in language in childhood associated with seizures or epileptiform electroencephalographic abnormalities. Despite an extensive literature, discrepancies and contradictions surround its definition and nosological boundaries. This paper reviews current conceptions of AEA and highlights variations in the aphasic disturbance, age of onset, epileptiform EEG abnormalities, temporal course, and long-term outcome. We suggest that AEA, rather than being a discrete entity, is comprised of multiple variants that have in common the features of language regression and epileptiform changes on EEG. Viewed this way, we argue that AEA can be conceptualized on a spectrum with other epileptiform neurocognitive disorders that may share pathophysiological features. The implications of this viewpoint are discussed, with emphasis on parallels between the AEA variants and regressive autistic spectrum disorders.

6.21. Nieminen-von Wendt, T., Salonen, O., Vanhala, R., Kulomaki, T., von Wendt, L., Autti, T. "A quantitative controlled MRI study of the brain in 28 persons with Asperger syndrome." *Int J Circumpolar Health.* 2002;61 Suppl 2:22-35. Publication Types: Clinical Trial, Controlled Clinical Trial.

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BACKGROUND: As structural brain abnormalities have been reported in infantile autism, the aim of this study was to determine whether such findings also exist in Asperger Syndrome (AS). **METHODS:** The diagnosis of Asperger Syndrome was based on the criteria in ICD-10 and DSM-IV. Brain magnetic resonance imaging (MRI) was performed with a 1.5 T imager. T2-weighted axial and coronal slices and T1-weighted three dimensional sagittal slices were obtained and visual and quantitative analysis were performed. **SUBJECTS:** There were 28 Asperger individuals, 17 children and adolescents (age 6-19 years, mean 12.4 years), 11 adults (age 20-60 years, mean 37.9 years) and 28 healthy age and gender matched controls. **RESULTS:** Mild inconsistent alterations were detected in 13/28 of the individuals with Asperger Syndrome compared to 6/23 in the comparable controls. There were no differences between the right and left hemispheres, nor was there any abnormality in terms of myelination or

migration. The anterior-posterior diameters of the mesencephalon were statistically significantly shorter in the Asperger syndrome individuals than in the controls. CONCLUSIONS: No consistent focal brain abnormalities for Asperger Syndrome were detected. The reduced diameters of the mesencephalon in the Asperger group support the hypothesis that the mesencephalon may be involved in the pathogenesis of Asperger Syndrome.

6.22. South, M., Williams, B.J., McMahon, W.M., Owley, T., Filipek, P.A., Shernoff, E., Corsello, C., Lainhart, J.E., Landa, R., Ozonoff, S. "Utility of the Gilliam Autism Rating Scale in research and clinical populations." *J Autism Dev Disord.* 2002 Dec;32(6):593-9. Publication Types: Validation Studies.

Department of Psychology, University of Utah, USA.

The Gilliam Autism Rating Scale (GARS) was developed as a relatively easy, inexpensive aid in the surveillance and diagnosis of autism. This study examined the validity of the GARS when used with a sample of 119 children with strict DSM-IV diagnoses of autism, ascertained from both clinical and research settings. The GARS consistently underestimated the likelihood that autistic children in this sample would be classified as having autism. The sample mean for the Autism Quotient, a hypothesized index of the likelihood of having autism, was 90.10, significantly below the reference mean of 100. Diagnostic classification according to criteria specified by the GARS resulted in a sensitivity of only .48. Limitations of rating scales in general and of the GARS specifically are discussed. It is recommended that clinicians and researchers using or considering using the GARS for autism diagnosis or ratings of autism severity recognize the need for further research regarding its use.

6.23. Noterdaeme, M., Mildenerger, K., Minow, F., Amorosa, H. "Evaluation of neuromotor deficits in children with autism and children with a specific speech and language disorder." *Eur Child Adolesc Psychiatry.* 2002 Oct;11(5):219-25.

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Several studies have described problems in motor functions in children with autism and children with a specific speech and language disorder. The purpose of this study was to identify neuromotor deficits in these neurodevelopmentally impaired children. A standardised neurological examination was performed in 11 children with childhood autism, 11 children with an expressive language disorder, 11 children with a receptive language disorder and 11 control children. The children were matched for age and non-verbal IQ, not for gender. All children had a non-verbal IQ above 85. The neurological examination procedure allowed for a qualitative and quantitative assessment of five specific neurological subsystems: fine and gross motor functions, balance, coordination and oral motor functions. The high-functioning children with autism and the children with a specific language disorder (expressive or receptive) had more motor problems

than the control children on most neurological subsystems. There were few statistically significant differences between the three groups of developmentally impaired children. The frequent co-occurrence of verbal and non-verbal, in particular neuromotor, deficits in developmentally impaired children put an additional burden on the development of these children and should be diagnosed as early as possible.

6.24. Maestro, S., Muratori, F., Cavallaro, M.C., Pei, F., Stern, D., Golse, B., Palacio-Espasa, F. "Attentional skills during the first 6 months of age in autism spectrum disorder." *J Am Acad Child Adolesc Psychiatry* 2002 Oct;41(10):1239-45.

Division of Child Neuropsychiatry, Scientific Institute Stella Maris, University of Pisa, Italy.

OBJECTIVE: To study the quality of early attention in autism spectrum disorder (ASD) through home movies. METHOD: Fifteen home movies from the first 6 months of life of children who later received a diagnosis of ASD were compared with home movies of 15 normal children. The diagnosis was performed after the third year of life of children by two senior child and adolescent psychiatrists using a checklist of symptoms according to the. The films of the two groups were mixed and rated by blind observers through a Grid for the Assessment of Attentional Skills in Infants, composed of 13 items grouped into three developmental areas. RESULTS: Using multivariate analysis of variance, the authors found significant differences between the two groups for the items in the social attention and the social behavior areas; on the contrary, there were no differences in nonsocial attention. CONCLUSIONS: The authors pose some hypotheses about a specific early-appearing impairment of attention in ASD in which children shift their spontaneous attention mainly toward nonsocial stimuli rather than toward social stimuli. The importance of this finding for early diagnosis and treatment is underlined.

6.25. Fatemi, S.H., Halt, A.R., Realmuto, G., Earle, J., Kist, D.A., Thuras, P., Merz, A. "Purkinje cell size is reduced in cerebellum of patients with autism." *Cell Mol Neurobiol* 2002 Apr;22(2):171-5.

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1. The authors' goal was to compare the size and density of Purkinje cells in the cerebellum of subjects with and without autism. Blocks of cerebellum were dissected at autopsy from the brains of age, sex- and postmortem-intervaled (PMI) groups of autistic and normal control individuals (N = 5 per group). Frozen, unfixed blocks were sectioned and stained with 1% cresyl violet. 2. The linear, molecular, granular densities and cross-sectional area of Purkinje cells were measured using computer-assisted image analysis. The average cross-sectional areas of Purkinje cells of the patients with autism were smaller by 24% when compared to the normal subjects. Two of the five autistic subjects had mean Purkinje cell sizes that corresponded to greater than 50% reduction in size. There was a substantial effect size difference

in Purkinje cell size ($\eta^2 = 0.29$) between control and autistic brains ($F(1, 8) = 3.32, P = 0.106$). No differences in Purkinje cell densities were observed between the two groups. These data indicate the possibility of Purkinje cell atrophy in autism with significant neurohistological heterogeneity among individuals diagnosed with this disorder.

6.26. Fatemi, S.H., Stary, J.M., Egan, E.A. "Reduced blood levels of reelin as a vulnerability factor in pathophysiology of autistic disorder." *Cell Mol Neurobiol* 2002 Apr;22(2):139-52.

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1. Autism is a severe neurodevelopmental disorder with potential genetic and environmental etiologies. Recent genetic linkage reports and biochemical analysis of postmortem autistic cerebellum point to Reelin, an important secretory extracellular protein, as being involved in the pathology of autism. 2. We hypothesized that blood levels of Reelin and its isoforms would be altered in autistic twins, and their first degree relatives versus normal controls. 3. We measured blood levels of unprocessed Reelin (410 kDa) and its proteolytic cleavage products (Reelins 330 and 180 kDa) as well as albumin and ceruloplasmin in 28 autistic individuals, their parents (13 fathers, 13 mothers), 6 normal siblings, and 8 normal controls using SDS-PAGE and western blotting. 4. Results indicated significant reductions in 410 kDa Reelin species in autistic twins (-70%, $p < 0.01$), their fathers (-62%, $p < 0.01$), their mothers (-72%, $p < 0.01$), and their phenotypically normal siblings (-70%, $p < 0.01$) versus controls. Reelin 330 kDa values did not vary significantly from controls. Reelin 180 kDa values for parents (fathers -32% $p < 0.05$ vs. controls, mothers -34%) declined when compared to controls. In contrast autistic Reelin 180 kDa increased, albeit nonsignificantly versus controls. Albumin and ceruloplasmin values for autistics and their first degree relatives did not vary significantly from controls. There were no significant meaningful correlations between Reelin, albumin and ceruloplasmin levels, age, sex, ADI scores, or age of onset. 5. These results suggest that Reelin 410 deficiency may be a vulnerability factor in the pathology of autism.

6.27. Bianchi, F.B., Muratori, P., Muratori, L. "New autoantibodies and autoantigens in autoimmune hepatitis." *Clin Liver Dis* 2002 Aug;6(3):497-509. Publication Types: Review, Review, Tutorial/

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The molecular characterization of the autoreactivities associated with autoimmune liver disease will improve their diagnosis and enhance understanding of their pathogenic mechanisms. Surprisingly, little is known about the nature of the major autoreactivities associated with type 1 AIH, including homogeneous ANA and antibodies to

microfilaments [3]. Type 1 AIH is, however, the prototype of autoimmune liver disease [103].

6.28. Blackwell, P.B. "Screening young children for autism and other social-communication disorders." *J Ky Med Assoc* 2002 Sep;100(9):390-4.

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Autism is a severe, multifaceted disorder of childhood that affects a large number of young children, causing social and communication disorders. Identification at a young age allows early treatment and the possibility of an improved outcome for these children and their families. This article reviews three screening instruments (Table 1): The Checklist for Autism in Toddlers (CHAT), the Modified Checklist for Autism in Toddlers (M-CHAT), and the Infant/Toddler Checklist of Communication and Language Development (CHECKLIST). These instruments may be used in the primary caregiver's office as an initial attempt to identify children who should be further examined for autism and other social-communication disorders.

6.29. Luna, B., Minshew, N.J., Garver, K.E., Lazar, N.A., Thulborn, K.R., Eddy, W.F., Sweeney, J.A. "Neocortical system abnormalities in autism: an fMRI study of spatial working memory." *Neurology* 2002 Sep 24;59(6):834-40.

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OBJECTIVE: To test the hypothesis that deficits in spatial working memory in autism are due to abnormalities in prefrontal circuitry. **METHODS:** Functional MRI (fMRI) at 3 T was performed in 11 rigorously diagnosed non-mentally retarded autistic and six healthy volunteers while they performed an oculomotor spatial working memory task and a visually guided saccade task. **RESULTS:** Autistic subjects demonstrated significantly less task-related activation in dorsolateral prefrontal cortex (Brodmann area [BA] 9/46) and posterior cingulate cortex (BA 23) in comparison with healthy subjects during a spatial working memory task. In contrast, activation of autistic individuals was not reduced in other regions comprising the neural circuitry for spatial working memory including the cortical eye fields, anterior cingulate cortex, insula, basal ganglia, thalamus, and lateral cerebellum. Autistic subjects also did not demonstrate reduced activation in any brain regions while performing visually guided saccades. **CONCLUSION:** Impairments in executive cognitive processes in autism may be subserved by abnormalities in neocortical circuitry as evidenced by decreased activation in prefrontal and posterior cingulate circuitry during a spatial working memory task.

6.30. Solaas, K.M., Skjeldal, O., Gardner, M.L., Kase, F.B., Reichelt, K.I.. "Urinary peptides in Rett syndrome." *Autism* 2002 Sep;6(3):315-28.

Institute of Pediatric Research, The National Hospital, University of Oslo, Norway.

Rett syndrome is a neuro-developmental disorder related to autistic behavior. Persons with autism have previously been found to have hyperpeptiduria. We here report a significantly higher level of peptides in the first fasting morning urine from 53 girls with Rett syndrome (both classical and congenital) compared with 53 healthy girls. This elevation in urinary peptides was similar to that in 35 girls with infantile autism. As in persons with autism, the individual levels of urinary peptides in the Rett syndrome group varied, and about a fifth were within the normal range. Levels of peptides were lower in girls with classic Rett syndrome than in girls with congenital Rett syndrome. This may be due to different etiological causes or to active and stagnant phases of the disease. Urine from girls with Rett syndrome was found to have higher frequency and higher levels of some urinary peptides that may cause inhibition of brain maturation and epilepsy

6.31. Kusaga, A., Yamashita, Y., Koeda, T., Hiratani, M., Kaneko, M., Yamada, S., Matsuishi, T. "Increased urine phenylethylamine after methylphenidate treatment in children with ADHD." *Ann Neurol* 2002 Sep;52(3):372-4.

Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume City, Japan.

The urine levels of beta-phenylethylamine, 3-methoxy-4-hydroxyphenyl glycol, homovanillic acid, and 5-hydroxyindoleacetic acid were measured to clarify the neurochemical mechanism in attention deficit hyperactivity disorder. beta-Phenylethylamine levels were significantly lower in attention deficit hyperactivity disorder individuals (n = 37) than in controls (n = 21). The 22 children with attention deficit hyperactivity disorder were treated with methylphenidate, and they were further divided into methylphenidate responders (n = 18) and nonresponders (n = 4). beta-Phenylethylamine levels significantly increased after methylphenidate therapy in responders, whereas they did not increase in nonresponders.

6.32. Vrancic, D., Nanclares, V., Soares, D., Kulesz, A., Mordzinski, C., Plebst, C., Starkstein, S. "Sensitivity and specificity of the autism diagnostic inventory-telephone screening in Spanish." *J Autism Dev Disord* 2002 Aug;32(4):313-20. Publication Types: Validation Studies.

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We report on the development in Argentina of a screening questionnaire for autism administered over the telephone. The Autism Diagnostic Inventory-Telephone Screening in Spanish (ADI-TSS) is based on the Autism Diagnostic Interview-Revised (ADI-R), keeping its structure but including fewer questions, which were rephrased to assess them over the telephone. The ADI-TSS went through different versions, with each modification gaining in reliability. The final version of the ADI-TSS could be assessed in 20 to 40 minutes and

demonstrated a high validity (using the ADI-R as the diagnostic gold-standard), high intrarater and interrater reliability (as measured with intraclass correlations), and high internal consistency (as measured with Cronbach's alpha). The validity of the ADI-TSS remained high when used by a health-related professional without formal training in the assessment of autistic patients. We believe the ADI-TSS is useful in field research studies as a screening instrument for patients with a potential diagnosis of autism, although future validation studies should include larger samples.

6.33. Cody, H., Pelphrey, K., Piven, J. "Structural and functional magnetic resonance imaging of autism." *Int J Dev Neurosci* 2002 Jun-Aug;20(3-5):421-38. Publication Types: Review, Review, Academic.

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Magnetic resonance imaging (MRI) of brain structures and function is uniquely suited to characterize the range of neuroanatomical and physiological changes that characterize the autism phenotype as it develops over time. In this review, we examine the scientific literature in MRI as applied to autism and related areas, over approximately the last decade, discussing findings which have emerged, methodological stumbling blocks which have been identified, and potential future directions. Structural MRI studies have recently begun to elucidate the neurodevelopmental underpinnings and brain-behavior relationships in autism while fMRI studies, building on the wealth of data in normal individuals, are beginning to characterize the underlying neuropsychological deficits of the disorder. Together, these two methods combine to contribute to a better understanding of the neural basis and brain phenotype of this disorder.

6.34. O'Brien, J., Spencer, J., Atkinson, J., Braddick, O., Wattam-Bell, J. "Form and motion coherence processing in dyspraxia: evidence of a global spatial processing deficit." *Neuroreport* 2002 Aug 7;13(11):1399-402.

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Form and motion coherence was tested in children with dyspraxia and matched controls to assess their global spatial and global motion processing abilities. Thresholds for detecting form coherence patterns were significantly higher in the dyspraxic group than in the control group. No corresponding difference was found on the motion coherence task. We tested eight children with dyspraxic disorder (mean age 8.2 years) and 50 verbal-mental-age matched controls (mean age 8.4 years) to test for a neural basis to the perceptual abnormalities observed in dyspraxia. The results provide evidence that children with dyspraxia have a specific impairment in the global processing of spatial information. This finding contrasts with other developmental disorders such as Williams syndrome, autism and dyslexia where deficits have been found in global motion processing and not global form processing. We conclude that children with

dyspraxia may have a specific occipitotemporal deficit and we argue that testing form and motion coherence thresholds might be a useful diagnostic tool for the often coexistent disorders of dyspraxia and dyslexia.

6.35. Parmeggiani, A., Posar, A., Giovanardi-Rossi, P., Andermann, F., Zifkin, B. "Autism, macrocrania and epilepsy: how are they linked?" *Brain Dev* 2002 Aug;24(5):296-9.

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To evaluate the possible association of autistic disorder (AD), macrocrania and epilepsy, we performed a retrospective study comparing epileptic and non-epileptic AD patients with macrocrania, and AD patients with macrocrania to age- and sex-matched AD controls without macrocrania. We found macrocrania in 17.3% of 121 patients with AD. Epilepsy was not significantly more frequent in AD patients with macrocrania than in those without macrocrania. There were no significant differences in the other clinical characteristics studied except for epileptiform EEG abnormalities which were more often found in AD patients with epilepsy. AD with macrocrania and epilepsy is not a syndrome but may be a marker for a group of subjects with AD. A role for familial macrocrania needs further assessment.

6.36. Gepner, B., Mestre, D.R. "Brief report: postural reactivity to fast visual motion differentiates autistic from children with Asperger syndrome." *J Autism Dev Disord* 2002 Jun;32(3):231-8.

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The aim of the present study was to search for a sensorimotor marker (i.e., visuopostural tuning) that could be correlated with the severity of motor impairments in children with autistic spectrum disorders. Given that autistic children were previously reported to be posturally hyporeactive to visually perceived environmental motion in comparison with normal control children (Gepner et al., 1995), we sought to determine whether children with Asperger syndrome (AS) would share the same postural hyporeactivity to visual motion. Three autistic children with mild to severe motor impairments, three AS children with soft motor signs, and nine normal control children were tested for overall postural instability and postural reactivity to environmental motion. Results indicate, first, that overall postural instability is significantly reduced in autistic children compared with both AS and normal children. Second, although postural oscillations in the fore-aft axis become more attuned to the oscillation frequency of an immersive dynamic visual display as visual speed is increased, in both control and AS subjects, this is not the case in autistic children. Despite the small number of subjects tested in this study, our data confirm the existence of a visuopostural detuning in autistic children. Third, they argue for a correlation between visuopostural tuning and severity of motor signs in children with autistic spectrum disorders. Finally, they

suggest a differentiation between children with autism and children with AS with regard to postural reactivity to fast visual motion. Neurophysiological implications of these results are discussed. In particular, a visuocerebellar pathway deficit hypothesis in autism is proposed.

6.37. Rutherford, M.D., Baron-Cohen, S., Wheelwright, S. "Reading the mind in the voice: a study with normal adults and adults with Asperger syndrome and high functioning autism." *J Autism Dev Disord* 2002 Jun;32(3):189-94.

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People with high functioning autism (HFA) and Asperger syndrome (AS) have deficits in theory of mind (ToM). Traditional ToM tasks are not sensitive enough to measure ToM deficits in adults, so more subtle ToM tests are needed. One adult level test, the Reading the Mind in the Eyes test has shown that AS and HFA subjects have measurable deficits in the ability to make ToM inferences. Here we introduce a test that extends the above task into the auditory domain and that can be used with adults with IQ Scores in the normal range. We report the use of the test with an adult sample of people with AS/HFA and with two adult control groups. Results suggest that individuals with AS/HFA have difficulty extracting mental state information from vocalizations. These results are consistent with previous results suggesting that people with HFA and AS have difficulties drawing ToM inferences.

6.38. Miranda-Linne, F.M., Melin, L. "A factor analytic study of the Autism Behavior Checklist." *J Autism Dev Disord* 2002 Jun;32(3):181-8.

Department of Psychology, University of Uppsala, Sweden.

The factor structure of the Autism Behavior Checklist (ABC) (Krug, Arick, & Almond, 1980a, 1980b), a 57-item screening instrument for autism, was examined on a sample of 383 individuals with autism spectrum disorders (i.e., autistic disorder, Asperger syndrome, and other autism-like conditions) aged 5-22 years. A five-factor model accounted for 80% of the total variance in the checklist. Thirty-nine of the 57 items had factor loadings of 0.4 or more, with 13 items loading on Factor 1, 11 items on Factor 2, 6 items on Factor 3, 5 items on Factor 4, and 4 items on Factor 5. No support was found for classifying the 57 items into the five subscales proposed by Krug et al. (1980a, 1980b) or for the three-factor solution suggested by Wadden, Bryson, and Rodger (1991).

6.39. Gross, T.F. "Perception of human and nonhuman facial age by developmentally disabled children." *J Autism Dev Disord* 2002 Jun;32(3):169-79.

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Human and nonhuman faces were shown to clinical controls, autistic, mentally retarded, and language-disordered children to assess their ability to detect and draw inferences about facial age. Children were asked to select from sets of three

faces the one that appeared youthful or to select faces that would be associated with some age-related characteristic. In two studies, it was found that, relative to other children, autistic children had more difficulty perceiving youthfulness in nonhuman faces compared with human faces. These data are discussed with respect to differences in mechanisms and processes that may underlie facial information processing in autistic and nonautistic children.

6.40. Tobing, L.F., Glenwick, D.S. "Relation of the childhood autism rating scale-parent version to diagnosis, stress, and age." *Res Dev Disabil* 2002 May-Jun;23(3):211-23.

Department of Psychology, Fordham University, Bronx, NY 10458-9993, USA.

This study explored the relation of severity of functional impairment on the Childhood Autism Rating Scale-Parent version (CARS-P) to diagnosis, parenting stress, and child age. Twenty-two mothers of children with autism and 19 mothers of children with pervasive developmental disorder-not otherwise specified (PDD-NOS) completed the CARS-P and the Parenting Stress Index. The autism group received significantly higher (i.e., more severe impairment) CARS-P ratings than did the PDD-NOS group. For the total sample, severity of impairment was a significant predictor of child-related parenting stress. The CARS-P was inconsistently associated with age-significantly positive for the PDD-NOS group but nonsignificantly for the autism group. Implications for the use of the CARS-P in assessment of children and the evaluation of interventions are discussed.

6.41. Phelan, A.I. "MMR and autism: an overview of the debate to date." *Br J Nurs* 2002 May 9-22;11(9):621-5.

Nursing Studies Department, Hatfield University, Hertfordshire.

The ongoing controversial debate about the measles mumps rubella (MMR) vaccine and its links to regression autism and specific bowel disorders appears to experience 'peaks and troughs' of public interest correlated with specific media attention at any one time. It is not the intention of this article to either refute or substantiate the ongoing controversy, as this is obviously a scientific debate, but rather to offer an overview of the studies to date in the interest of helping practitioners in the frontline to engage in informed debate with concerned parents. The conclusions from this review stem from two major studies conducted by the Institute of Medicine (IoM, 2001) in the USA, and Medical Research Council (MRC, 2001) in the UK. Both conclude that although epidemiological studies so far do not support a link between MMR and autism, nonetheless the studies have been too imprecise to rule out the prospect of the vaccination being involved in a small number of cases, and the need for further research has been pointed out.

6.42. Gillberg, C., de Souza, L. "Head circumference in autism, Asperger syndrome, and ADHD: a comparative study." *Dev Med Child Neurol* 2002 May;44(5):296-300. Publication Types: Clinical Trial Controlled Clinical Trial

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This study was undertaken to test the hypothesis that children with autistic spectrum disorders often have macrocephalus, and that those without comorbid learning disability are most frequently affected. Fifty consecutive children with Asperger syndrome (45 males, five females; mean age 9 years, range 1 year 6 months to 16 years) without indications of underlying medical disorders were matched for birth year and sex with 50 children (45 males, five females; mean age 6 years 4 months, range 1 year 4 months to 13 years 11 months) who met criteria for autistic disorder (a lower-functioning disorder within the autism spectrum) and with 50 children (45 males, five females; mean age 8 years 4 months, range 1 year 6 months to 15 years 5 months) who met criteria for attention-deficit-hyperactivity disorder. Birth and neuropsychiatric follow-up records were examined and data relating to occipitofrontal circumference, weight, and height were detailed. The group with Asperger syndrome included a subset of individuals with macrocephalus recorded both at birth and at follow-up after the first year of life. Another subgroup developed macrocephalus during early childhood. Autistic spectrum disorders include a subgroup with macrocephalus characterized by a relatively high level of functioning and a clinical presentation most often consistent with a diagnosis of Asperger syndrome.

6.43. Leask, J. "Vaccination and risk communication: summary of a workshop, Arlington Virginia, USA, 5-6 October 2000." *J Paediatr Child Health* 2002 Apr;38(2):124-8. Publication Types: Congresses.

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The declining incidence of vaccine-preventable diseases has led to an increased public focus on the issue of vaccine safety. In an environment of increased consumerism, interest in alternative health practices and anti-vaccination lobbying, media reports that call into question the safety of scheduled vaccines can significantly raise parents' concerns. Recent media coverage of a suggested but unproved link between the measles-mumps-rubella vaccine and autism has highlighted the challenges of providing a consistent and coordinated response. For those concerned about effectively communicating the benefits and risks of vaccination, the field of risk communication can provide helpful insights. This paper summarizes the Workshop on Vaccine Communication held in the USA during October 2000. It highlights the perspectives given by consumers, providers, journalists and risk-communication experts and discusses implications for Australia. These centre around how government and health professionals might respond to vaccine safety scares in the public arena, and to parental concerns raised in clinical encounters. Finally, the potential risks and benefits of engaging with the anti-vaccination lobby are outlined.

6.44. Osterling, J.A., Dawson, G., Munson, J.A. "Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation." *Dev Psychopathol* 2002 Spring;14(2):239-51.

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Previous work based on observations of home videotapes indicates that differences can be detected between infants with autism spectrum disorder and infants with typical development at 1 year of age. The present study addresses the question of whether autism can be distinguished from mental retardation by 1 year of age. Home videotapes of first birthday parties from 20 infants later diagnosed with autism spectrum disorder, 14 infants later diagnosed with mental retardation (without autism), and 20 typically developing infants were coded by blind raters with respect to the frequencies of specific social and communicative behaviors and repetitive motor actions. Results indicated that 1-year-olds with autism spectrum disorder can be distinguished from 1-year-olds with typical development and those with mental retardation. The infants with autism spectrum disorder looked at others and oriented to their names less frequently than infants with mental retardation. The infants with autism spectrum disorder and those with mental retardation used gestures and looked to objects held by others less frequently and engaged in repetitive motor actions more frequently than typically developing infants. These results indicate that autism can be distinguished from mental retardation and typical development by 1 year of age.

6.45. Thirumalai, S.S., Shubin, R.A., Robinson, R. "Rapid eye movement sleep behavior disorder in children with autism." *J Child Neurol* 2002 Mar;17(3):173-8.

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We performed nocturnal polysomnography on 11 children with autism who had symptoms of disrupted sleep and nocturnal awakenings. We identified rapid eye movement (REM) sleep behavior disorder in 5 of these 11 patients. Since REM sleep behavior disorder typically affects elderly males with neurodegenerative diseases, the identification of this phenomenon in autistic children could have profound implications for our understanding of the neurochemical and neurophysiologic bases of autism. Further, accurate diagnosis of REM sleep behavior disorder would enable specific treatment with clonazepam and help the family and the child consolidate sleep and improve daytime performance.

6.46. Grady, C.L., Keightley, M.L. "Studies of altered social cognition in neuropsychiatric disorders using functional neuroimaging." *Can J Psychiatry* 2002 May;47(4):327-36. Publication Types: Review Review, Tutorial

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In this paper, we review studies using functional neuroimaging to examine cognition in neuropsychiatric disorders. The focus is on social cognition, which is a topic that has received increasing attention over the past few years. A network of brain regions is proposed for social cognition that includes regions involved in processes relevant to social functioning (for example, self reference and emotion). We discuss the alterations of activity in these areas in patients with autism, depression, schizophrenia, and posttraumatic stress disorders in relation to deficits in social behaviour and symptoms. The evidence to date suggests that there may be some specificity of the brain regions involved in these 4 disorders, but all are associated with dysfunction in the amygdala and dorsal cingulate gyrus. Although there is much work remaining in this area, we are beginning to understand the complex interactions of brain function and behaviour that lead to disruptions of social abilities.

6.47. Stanley, J.A. "In vivo magnetic resonance spectroscopy and its application to neuropsychiatric disorders." *Can J Psychiatry* 2002 May;47(4):315-26. Publication Types: Review, Review, Tutorial

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In vivo magnetic resonance spectroscopy (MRS) is the only noninvasive imaging technique that can directly assess the living biochemistry in localized brain regions. In the past decade, spectroscopy studies have shown biochemical alterations in various neuropsychiatric disorders. These first-generation studies have, in most cases, been exploratory but have provided insightful biochemical information that has furthered our understanding of different brain disorders. This review provides a brief description of spectroscopy, followed by a literature review of key spectroscopy findings in schizophrenia, affective disorders, and autism. In schizophrenia, phosphorus spectroscopy studies have shown altered metabolism of membrane phospholipids (MPL) during the early course of the illness, which is consistent with a neurodevelopmental abnormality around the critical period of adolescence when the illness typically begins. Children and adolescents who are at increased genetic risk for schizophrenia show similar MPL alterations, suggesting that schizophrenia subjects with a genetic predisposition may have a premorbid neurodevelopmental abnormality. Independent of medication status, bipolar subjects in the depressive state tended to have higher MPL precursor levels and a deficit of high-energy phosphate metabolites, which also is consistent with major depression, though these results varied. Further bipolar studies are needed to investigate alterations at the early stage. Lastly, associations between prefrontal metabolism of high-energy phosphate and MPL and neuropsychological performance and reduced N-acetylaspartate in the temporal and cerebellum regions have been reported in individuals with autism. These findings are consistent with developmental alterations in the temporal lobe and in the cerebellum of persons with autism. This paper discusses recent findings of new functions of N-acetylaspartate.

6.48. Bolton, P.F., Park, R.J., Higgins, J.N., Griffiths, P.D., Pickles, A. "Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex." *Brain* 2002 Jun;125(Pt 6):1247-55.

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Tuberous sclerosis is one of the few established medical causes of autism spectrum disorder and is a unique neurogenetic model for testing theories about the brain basis of the syndrome. We conducted a retrospective case study of the neuro-epileptic risk factors predisposing to autism spectrum disorder in individuals with tuberous sclerosis to test current neurobiological theories of autism spectrum disorder. We found that an autism spectrum disorder diagnosis was associated with the presence of cortical tubers in the temporal but not other lobes of the brain. Indeed, the presence of tubers in the temporal lobes appeared to be a necessary but not sufficient risk factor for the development of an autism spectrum disorder. However, contrary to the predictions of some theories, the location of tubers in specific regions of the temporal lobe, such as the superior temporal gyrus or the right temporal lobe, did not determine which individuals with temporal lobe tubers developed an autism spectrum disorder. Instead, outcome was associated with various indices of epileptic activity including evidence of temporal lobe epileptiform discharges on EEG, the age to onset of seizures in the first 3 years of life and a history of infantile spasms. The results indicated that individuals with tuberous sclerosis are at very high risk of developing an autism spectrum disorder when temporal lobe tubers are present and associated with temporal lobe epileptiform discharges and early-onset, persistent spasm-like seizures. These risk markers constitute useful clinical indicators of prognosis, but further research is required to identify the neurobiological mechanisms responsible for their association with outcome. Most especially, it will be important to test whether, as the findings suggest, there is a critical early stage of brain maturation during which temporal lobe epilepsy perturbs the development of brain systems that underpin 'social intelligence' and possibly other cognitive skills, thereby inducing an autism spectrum disorder.

6.49. Curatolo, P., Verdecchia, M., Bombardieri, R. "Tuberous sclerosis complex: a review of neurological aspects." *Eur J Paediatr Neurol* 2002;6(1):15-23. Publication Types: Review, Tutorial.

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Tuberous sclerosis complex is characterized by hamartomatous lesions involving skin, brain, kidneys, eyes and heart. Pathologically, tuberous sclerosis is a disorder of cell migration, proliferation and differentiation. Cell lineage and cell migration disorders in the developing cortex of tuberous sclerosis complex patients might produce very different neurological phenotypes including epilepsy, cognitive impairment and autism. Cortical tubers constitute

the hallmark of the disease and are pathognomonic of cerebral tuberous sclerosis. Epilepsy is the most common neurological feature, occurring in 96% of patients. Seizures often begin in the first months of life and are frequently severe and intractable. The treatment of seizures has recently benefited from the advent of the new anti-epileptic drugs. Selected drug-resistant patients with tuberous sclerosis complex could be considered for surgical treatment. Clear localization of the most active epileptogenic focus and the zone of the cortical abnormality may lead to tubectomy and improved seizure control in selective drug-resistant patients. The finding of multiple areas of cerebral involvement should not automatically preclude epilepsy surgery in a child with intractable seizures and a well defined seizure origin.

6.50. Torrente, F., Ashwood, P., Day, R., Machado, N., Furlano, R.I., Anthony, A., Davies, S.E., Wakefield, A.J., Thomson, M.A., Walker-Smith, J.A., Murch, S.H. "Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism." *Mol Psychiatry* 2002;7(4):375-82, 334.

Centre for Paediatric Gastroenterology, Royal Free & University College Medical School, London, UK.

We have reported lymphocytic colitis in children with regressive autism, with epithelial damage prominent. We now compare duodenal biopsies in 25 children with regressive autism to 11 with coeliac disease, five with cerebral palsy and mental retardation and 18 histologically normal controls. Immunohistochemistry was performed for lymphocyte and epithelial lineage and functional markers. We determined the density of intraepithelial and lamina propria lymphocyte populations, and studied mucosal immunoglobulin and complement C1q localisation. Standard histopathology showed increased enterocyte and Paneth cell numbers in the autistic children. Immunohistochemistry demonstrated increased lymphocyte infiltration in both epithelium and lamina propria with upregulated crypt cell proliferation, compared to normal and cerebral palsy controls. Intraepithelial lymphocytes and lamina propria plasma cells were lower than in coeliac disease, but lamina propria T cell populations were higher and crypt proliferation similar. Most strikingly, IgG deposition was seen on the basolateral epithelial surface in 23/25 autistic children, co-localising with complement C1q. This was not seen in the other conditions. These findings demonstrate a novel form of enteropathy in autistic children, in which increases in mucosal lymphocyte density and crypt cell proliferation occur with epithelial IgG deposition. The features are suggestive of an autoimmune lesion.

6.51. Casanova, M.F., Buxhoeveden, D.P., Switala, A.E., Roy, E. "Asperger's syndrome and cortical neuropathology." *J Child Neurol* 2002 Feb;17(2):142-5.

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Asperger's disorder or syndrome is characterized by impaired social interaction, normal intelligence, and adequate language

skills in the areas of grammar and vocabulary. The symptoms are pervasive in nature and usually manifested in childhood. Despite the gravity and chronicity of the condition, the medical literature remains sparse and offers no information about possible neuropathologic underpinnings. The present study is a case report on two patients with Asperger's syndrome. Neuropathologic examination revealed no degenerative changes or gliosis. A more detailed assessment with computerized image analysis indicated abnormalities in the minicolumnar organization of the three areas examined (9, 21, 22) ($P = .032$). Specifically, minicolumns were smaller, and their component cells were more dispersed than normal. A similar neuropathology has recently been reported for autism and disputes the uniqueness of these findings. The minicolumnar changes provide a possible link to receptive field abnormalities and a useful clinicopathologic correlate to Asperger's syndrome.

6.52. Charman, T., Baird, G. "Practitioner review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children." *J Child Psychol Psychiatry* 2002 Mar;43(3):289-305. Publication Types: Review, Review, Tutorial.

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BACKGROUND: Progress has recently been made in the earlier identification of children with autism spectrum disorder (ASD). Whilst being welcome, this progress to earlier referral and diagnosis presents new challenges to clinical practice, including the accuracy and stability of early diagnosis, the utility of standardised assessment instruments with young pre-schoolers and the ability to indicate prognosis. **METHOD:** A selective review of recent research literature on the characteristic features of ASD in preschool children. **RESULTS:** Multidisciplinary diagnostic assessment should include detailed information on developmental history, parents' descriptions of the everyday behaviour and activities of the child, direct assessment of the child's social interaction style, including where possible with age peers, and formal assessment of communicative, intellectual and adaptive function. Clinical assessments need to concentrate on the identification of impairments in early non-verbal social communication behaviours that characterise children with ASD from the second year of life, including social orienting, joint attention, imitation, play and reciprocal affective behaviour. The particular pattern of symptoms that presents in a 2-year-old with ASD may differ from that seen at the more prototypic age of 4 or 5 years. In particular, overt repetitive and stereotyped behaviours may be less notable, although where these are seen alongside the social and communicative impairments they are highly indicative of ASD. The use of standardised assessment instruments and the strict application of the DSM and ICD diagnostic criteria need to be employed with caution, as an expert clinical view has been shown to be more accurate. An important aspect of early diagnostic consultation is an open and straightforward approach to the negotiation of the diagnostic view with parents over time. **CONCLUSIONS:** Earlier diagnosis and rising recognition of ASD have significant implications for

primary healthcare and specialist diagnostic and therapeutic services.

6.53. Zappella, M. "Early-onset Tourette syndrome with reversible autistic behaviour: a dysmaturational disorder." *Eur Child Adolesc Psychiatry* 2002 Feb;11(1):18-23.

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Early-onset Tourette syndrome comorbid with reversible autistic behaviour is described in twelve young males. After a normal gestation, delivery and first-year development, regression set in between the age of one and two with loss of various abilities and the emergence of autistic behaviour. At this time, or slightly later, they showed multiple motor and vocal tics, simple and complex: the latter could also be traced to most of their parents. Following an intervention based on intense cuddling, motor activation and paedagogic guidance, these children's abilities rapidly improved, reaching at follow-up a normal or borderline intellectual functioning and with the disappearance of their initial autistic behaviour. At follow-up tics were present in all, usually with the features of a full-blown Tourette syndrome, often comorbid with ADHD, and in some cases with OCD.

6.54. Tang, J.C., Kennedy, C.H., Koppekin, A., Caruso, M. "Functional analysis of stereotypical ear covering in a child with autism." *J Appl Behav Anal* 2002 Spring;35(1):95-8.

Vanderbilt University, Nashville, Tennessee 37203, USA.

We studied stereotypical ear covering in a child with autism. Results of a descriptive analysis were inconclusive but revealed a correlation between ear covering and another child's screaming. An analogue functional analysis showed that ear covering was emitted only when the screaming was present.

6.55. Topcu, M., Saatci, I., Haliloglu, G., Kesimer, M., Coskun, T. "D-glyceric aciduria in a six-month-old boy presenting with West syndrome and autistic behaviour." *Neuropediatrics* 2002 Feb;33(1):47-50.

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D-Glyceric aciduria is a disease with a very heterogeneous group of symptoms, with D-glyceric acid excretion as the chief common characteristic. Findings described in previous patients include progressive neurological impairment, hypotonia, seizures, failure to thrive and metabolic acidosis. However, there are also asymptomatic patients with mild neurological impairment. A six-month-old boy was admitted to our clinic with the complaints of dullness to his environment, seizures and autistic behaviour. EEG revealed multifocal generalized epileptic activity in a hypsarrhythmia pattern. Organic acid analysis (GC-MS) in urine revealed increased glyceric acid excretion. Analysis of the optical form of glyceric acid by a polarimetric method supported the diagnosis of D-glyceric aciduria. MRI showed white matter lesions with cerebral atrophy, particularly in the

frontotemporal regions, and reversible abnormalities in the mesencephalon, thalami and globus pallidum resolving after fructose restriction in the diet. To our knowledge, this is the first case report of a patient with D-glyceric aciduria who presented with West syndrome and autistic behaviour in whom serial MRI findings are also defined.

6.56. Daley, T.C., Sigman, M.D. "Diagnostic conceptualization of autism among Indian psychiatrists, psychologists, and pediatricians." *J Autism Dev Disord* 2002 Feb;32(1):13-23.

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Diagnostic criteria for autism and background characteristics used by 937 Indian psychiatrists, psychologists and pediatricians were examined. Participants were asked to rate 18 behaviors as necessary for a diagnosis of autism, helpful but not necessary, or not helpful in a diagnosis of autism, and were asked to provide other information about their experiences with autism. Professionals' experience with diagnosing cases did not vary by profession and, in general, the three professions agreed about the characteristics most necessary for a diagnosis. However, within-group differences were found on the agreement over the usefulness of individual characteristics and amount of experience diagnosing cases as autistic. Comparisons with DSM-III and DSM-IV criteria suggest that Indian professionals may adhere to these systems. Conclusions about diagnosis in a cultural context and areas for future research are suggested.

6.57. Milne, E., Swettenham, J., Hansen, P., Campbell, R., Jeffries, H., Plaisted, K. "High motion coherence thresholds in children with autism." *J Child Psychol Psychiatry* 2002 Feb;43(2):255-63.

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BACKGROUND: We assessed motion processing in a group of high functioning children with autism and a group of typically developing children, using a coherent motion detection task. **METHOD:** Twenty-five children with autism (mean age 11 years, 8 months) and 22 typically developing children matched for non-verbal mental ability and chronological age were required to detect the direction of moving dots in a random dot kinematogram. **RESULTS:** The group of children with autism showed significantly higher motion coherence thresholds than the typically developing children (i.e., they showed an impaired ability to detect coherent motion). **CONCLUSIONS:** This finding suggests that some individuals with autism may show impairments in low-level visual processing—specifically in the magnocellular visual pathway. The findings are discussed in terms of implications for higher-level cognitive theories of autism, and the suggestion is made that more work needs to be carried out to further investigate low-level visual processing in autism.

6.58. Anderson, R.J., Bendell, D.J., Garnett, I., Groundwater, P.W., Lough, W.J., Mills, M.J., Savery, D., Shattock, P.E. "Identification of indolyl-3-acryloylglycine in the urine of people with autism." *J Pharm Pharmacol* 2002 Feb;54(2):295-8.

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HPLC analysis of the urine of autistic subjects indicated the presence of an unidentified component in greatly increased concentrations. We have reported the isolation of this component by HPLC and its identification. Mass spectrometry, NMR and UV spectroscopy identified the peak as corresponding to indolyl-3-acryloylglycine (IAG, 3), and this has been confirmed by an independent synthesis.

6.59. McQueen, J.M., Heck, A.M. "Secretin for the treatment of autism." *Ann Pharmacother* 2002 Feb;36(2):305-11. Publication Types: Review, Review, Tutorial.

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OBJECTIVE: To evaluate the role of secretin in the treatment of children with autism. **DATA SOURCE:** Literature was assessed through MEDLINE, EMBASE, BIOSIS (November 1998-August 2001), and the World Wide Web. Literature included scientific studies, anecdotal reports, and meeting abstracts. Key search terms included autism and secretin. **DATA SYNTHESIS:** Autism is a pervasive developmental disorder. Although several treatments exist, no cure has been identified. New information suggests that secretin may be beneficial for this disorder. A critical evaluation of current information about the use of secretin in autism was conducted. **CONCLUSIONS:** Currently, several anecdotal reports and a few controlled trials with conflicting results have been published regarding the use of secretin in autism. Further studies should be conducted to determine the safety and efficacy of secretin for autism.

6.60. Boddaert, N., Zilbovicius, M. "Functional neuroimaging and childhood autism." *Pediatr Radiol* 2002 Jan;32(1):1-7. Publication Types: Review, Review, Tutorial.

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Childhood autism is now widely viewed as being of developmental neurobiological origin. Yet, localised structural and functional brain correlates of autism have to be established. Structural brain-imaging studies performed in autistic patients have reported abnormalities such as increased total brain volume and cerebellar abnormalities. However, none of these abnormalities fully account for the full range of autistic symptoms. Functional brain imaging, such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional MRI (fMRI)

have added a new perspective to the study of normal and pathological brain functions. In autism, functional studies have been performed at rest or during activation. However, first-generation functional imaging devices were not sensitive enough to detect any consistent dysfunction. Recently, with improved technology, two independent groups have reported bilateral hypoperfusion of the temporal lobes in autistic children. In addition, activation studies, using perceptive and cognitive paradigms, have shown an abnormal pattern of cortical activation in autistic patients. These results suggest that different connections between particular cortical regions could exist in autism. The purpose of this review is to present the main results of rest and activation studies performed in autism.

6.61. Blackwell, J. "Clinical practice guideline: screening and diagnosing autism." *J Am Acad Nurse Pract* 2001 Dec;13(12):534-6.

The clinical practice guideline (CPG) reviewed in this month's column concerns the screening and diagnosis of autism. Autism is the third most common developmental disability and affects more than 1 in 500 children, or nearly 400,000 people in the United States, in some form. Primary care providers of children, including pediatric nurse practitioners (PNPs) and family nurse practitioners (FNPs), should reasonably expect to care for at least one child with autism (CWA). The American Academy of Neurology (AAN) has therefore developed guidelines to help healthcare providers facilitate the early identification of children with autism.

6.62. Schumann, C.M., Buonocore, M.H., Amaral, D.G. "Magnetic resonance imaging of the post-mortem autistic brain." *J Autism Dev Disord* 2001 Dec;31(6):561-8.

The MIND Institute, Department of Psychiatry, University of California, Davis 95616, USA.

Magnetic resonance imaging (MRI) is a valuable, noninvasive tool for understanding structural abnormalities in the brain. The M.I.N.D. Institute at UC Davis has developed a protocol utilizing MRI to investigate anatomical differences in the post-mortem brain by applying a proton density weighted imaging sequence for optimal differences in image intensity (contrast) between gray and white matter. Images of the brain obtained prior to distribution of tissue and further neuropathological examination provide a record of how the brain appeared prior to tissue processing. The virtual representation of the whole brain can also be subjected to additional analyses, such as measuring the volume of brain regions or area of the cortical surface. We describe our procedures for carrying out post-mortem MRI of the human brain.

6.63. Mildenberger, K., Sitter, S., Noterdaeme, M., Amorosa, H. "The use of the ADI-R as a diagnostic tool in the differential diagnosis of children with infantile autism and children with a receptive language disorder." *Eur Child Adolesc Psychiatry* 2001 Dec; 10(4): 248-55.

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Children with infantile autism and children with a specific receptive language disorder often show similar behavioural problems, making the differentiation between these two diagnostic categories difficult. The purpose of this study is to evaluate the usefulness of parental information in the differential diagnosis of the two types of disorders mentioned above. Sixteen children with a receptive language disorder and 11 children with infantile autism participated in the study. All children had normal non-verbal IQs. The ADI-R (Autism Diagnostic Interview - Revised) was performed with all children. The results showed that the ADI-R items reflecting behavioral features at pre-school age (age range 4-5 years) were better suited to differentiate the groups than the items reflecting behavioral features at the time of the investigation (mean age: 9 years). The items on the dimension "Reciprocal social interaction" and "Communication and language" According to the ICD-10 algorithm of the ADI-R one child with autism and one child with a receptive language disorder were falsely classified. These false classifications were mainly due to a distorted parental perception of the child's behaviour. The ADI-R is a useful tool in the differential diagnosis of developmental disorders.

6.64. Koenig, K., Scahill, L. "Assessment of children with pervasive developmental disorders." *J Child Adolesc Psychiatry Nurs* 2001 Oct-Dec; 14(4): 159. Publication Types: Review, Review, Tutorial.

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TOPIC: Pervasive developmental disorders, a group of conditions marked by impaired social reciprocity, communication deficits, and restricted, repetitive behaviors. PURPOSE: Advanced practice nurses (APNs) are in a unique position to assess these children, make an appropriate diagnosis, and refer parents for further consultation and intervention. SOURCES: Current literature, formal training on diagnostic instruments, and clinical experience. CONCLUSIONS: Diagnosis of pervasive developmental disorders requires knowledge of normal growth and development and other childhood psychiatric disorders. The role of the APN includes counseling parents regarding their child's legal right to intervention and guiding parents to make empirically based choices for intervention.

6.65. Scambler, D., Rogers, S.J., Wehner, E.A. "Can the checklist for autism in toddlers differentiate young children with autism from those with developmental delays?" *J Am Acad Child Adolesc Psychiatry* 2001 Dec;40(12): 1457-63. Publication Types: Validation Studies.

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OBJECTIVE: The Checklist for Autism in Toddlers (CHAT) has been demonstrated to be sensitive to the presence of autism in otherwise normally developing 18-month-old children. However, its ability to differentiate autism from other significant developmental delays is unknown. This study

examined this question. **METHOD:** The CHAT was applied to a group of 44 children aged 2 and 3 years, rigorously diagnosed with autism or with other developmental problems. **RESULTS:** By the original CHAT author's criteria, the sensitivity and specificity of the CHAT were 65% and 100 % Respectively. Slightly altering the criteria resulted in a sensitivity of 85% in the current group of children with developmental disabilities while maintaining specificity of 100%. **CONCLUSIONS:** The current study is the first to demonstrate that the CHAT successfully discriminates 2 year-old children with autism from those with other developmental disabilities may improve its usefulness as a screening tool for community-based early-diagnostic teams and general practitioners.

6.66. Gotoh, H., Suzuki, I., Maruki, K., Mitomo, M., Hirasawa, K., Sasaki, N. "Magnetic resonance imaging and clinical findings examined in adulthood - studies on three adults with Rett syndrome." *Brain Dev* 2001 Dec;23 Suppl 1: S118-21.

Department of Pediatrics, Hikarino -ie Institute, Moro Hospital, 38 Morohongou, Iruma-gum, 350-0495, Saitama, Japan.

Purpose : To clarify magnetic resonance imaging (MRI) findings in three adult patients with Rett syndrome who had been diagnosed with mental retardation and autism. **Method :** Clinical and MRI findings in three adult cases with Rett syndrome were studied . Ages (in years) in three adult cases with Rett syndrome were 46 in Case 1, 35 in Case 2 and 20 in Case 3. They were able to walk and their convulsions were well controlled **Results:** MRI findings in all patients showed mild cerebral atrophy, especially in the frontal and temporal lobes and two of the cases also had mild cerebellar atrophy. One Case also showed a narrowing of the brainstem and thinning of the corpus callosum, may be due to congenital hypoplasia. It was also seen that cerebellar atrophy became more distinct in older cases.

6.67. Zwaigenbaum, L. "Autistic Spectrum disorders in preschool children." *Can Fam Physician* 2001 Oct; 47: 2037 - 42. Publication Types:Review, Review, Tutorial.

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OBJECTIVE: To review existing data on early signs of autistic spectrum disorders (ASD) and on how these disorders can be distinguished from other atypical patterns of development, and to describe a developmental surveillance approach that family physicians can use to ensure that children with these diagnoses are detected as early as possible. **QUALITY OF EVIDENCE:** MEDLINE was searched from January 1966 to July 2000 using the MeSH terms autistic disorder/diagnosis AND diagnosis, differential AND (infant OR child, preschool). Articles were selected based on relevance to developmental surveillance in primary care and on experimental design, with emphasis on prospective studies with systematic measurement procedures using up to date diagnostic criteria. **MAIN MESSAGE:** Autistic spectrum

disorders are characterized by impairments in social interaction and verbal and non verbal communication, and by preferences for repetitive interests and behaviors. Early signs that distinguish ASD from other atypical patterns of development include poor use of eye gaze, lack of gestures to direct other people's attention (particularly to show things of interest), diminished social responsiveness, and lack of age - appropriate play with toys (especially imaginativ use of toys).Careful attention to parents' concerns and specific inquiry into and observation of how children interact, communicate, and play will help ensure that early signs are detected during regular health maintenance visits. **CONCLUSIONS:** Family physicians have an important role in early identification of children with ASD. Early diagnosis of these disorders is essential to ensure timely access to interventions known to improve outcomes for these children.

6.68. Adreïn, J.L., Roux, S., Couturier, G., Malvy, J., Guerin, P., Debuly, S., Lelord, G., Barthelemy, C. "Towards a new functional assesment of autistic dysfunction in children with developmental disorders: the Behaviour Function Inventory." *Autism* 2001 Sep; 5(3): 249-64.

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In order to asses particular disorders of psychological development and functioning in children with developmental disorders, we have developed a new tool, the Behaviour Function Inventory (BFI), based on 11 neurophysiological functions, disorders of which are considered to contribute to the core autistic syndrome. This article reports the reliability and validity study of this new scale. Factorial analysis computed on the 55 initial items identified six main dimensions which we characterized and labelled: interaction dysfunction, praxis dysfunction, auditory dysfunction, islet of ability and emotional dysfunction. Relationships between these six new variables and diagnostic subgroups, and chronological and developmental age, are discussed. The BFI offers precise information of the functional symptomatology of autism, showing clear evidence of some disordered areas of functioning. This new approach may provide valuable information in clinical research, especially for psychopathology and physiopathology studies.

6.69. Mayes, S.D., Calhoun, S.L. "Non-significance of early speech delay in children with autism and normal intelligence and implications for DSM-IV Asperger's disorder." *Autism* 2001 Mar; 5(1): 81-94.

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According to the DSM-IV, children with Asperger's disorder do not have significant cognitive or speech delays, whereas children with autistic disorder may or may not. In our study, children with normal intelligence who had clinical diagnoses of autism or Asperger syndrome were divided into two groups that would support absence of speech delay as a DSM - IV criterion for Asperger's disorder. No significant differences were found between the 23 children with a speech delay and

the 24 children without a speech delay on any of the 71 variables analyzed, including autistic symptoms and expressive language. Results suggest that early speech delay may be irrelevant to later functioning in children who have normal intelligence and clinical diagnoses of autism or Asperger syndrome and that speech delay as a DSM -IV distinction between Asperger's disorder and autism may not be justified.

6.70. Gillberg, C., Gillberg, C., Rastam, M., Wentz, E. "The Asperger's Syndrome (and high - functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview." *Autism* 2001 Mar; 5(1): 57-66.

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The Development of the Asperger syndrome (and high-functioning autism) Diagnostic Interview (ASDI) is described. Preliminary data from a clinical study suggest that inter-rater reliability and test-retest stability may be excellent, with kappas exceeding 0.90 in both instances. The validity appears to be relatively good. No attempt was made in the present study to validate the instrument as regards the distinction between Aspergers syndrome and high-functioning autism.

6.71. Frank, Y., Pavlakis, S.G. "Brain imaging in neuro behavioral disorders." *Pediatr Neurol* 2001 Oct;25(4):278-87. Publication Types: Review, Review, Tutorial.

Child Study Centre, Bronx Lebanon Hospital Centre, Bronx, New York 10457,USA.

Neuroimaging studies of nerobehaviral disorders are using new imaging modalities. In dyslexia, anatomic imaging studies demonstrate an abnormal symmtery of the planum temporate. Functional imaging demonstates temporal lobe abnormalities and abnormal interaction between frontal and parietal brain areas. In attention -deficit- hyperactivity disorder, imaging studues suggest an abnormality in the prefrontal and striatal regions. Neuroimaging studies are often contradictory, but trends, especially with functional imaging analysis, are evolving. Beacause nerobehaviral disorders seem to be a result of a dysfunction in brain circuits, no one region will be abnormal in all patients studied. Further studies with welldefined patient populations and appropriate activation paradigms will better elucidate the pathophysiology of thse conditions.

6.72. Muratori, F., Cessari, A., Casella, C. "Autism and cerebellum. An unusual finding with MRI." *Panminerva Med* 2001 Dec; 43(4): 311-5. Publication Types:Review, Review, Tutorial.

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In recent years neuroimaging techniques have shown in young autistic children morphological disorders of the brain stem and cerebellum. After a review of the literature the authors

present a three -year old child, with a pervasive developmental disorder (autistic type) whose MRI shows unusual finding in the right cerebellar hemisphere. The acheived levels in many developmental areas (linguistic, cognitive, relational, communicative) have been referred too. This developmental description represents additional information to the research about possible correlations between autistic sytoms and neuromatic such as joint attention, cognitive and linguistic functions which are probably involved in pathogenesis of autistic disorder. The presence of such inabilities in a case with cerebellar hemisphere abnormalities,without vermis compromission, could suggest that in autism exist deficits in more complex connections between neocerebellum and others regions of the brain.

6.73. Flanagan, O., Nuallain, S.O. "A study looking at the effectiveness of developmental screening in identifying learning disabilities in early childhood." *Ir Med J* 2001 May;94(5):148-50.

Brothers of Charity Early Intervention Services, Lower Newcastle, Galway.

This is a retrospective study of children under six years of age referred to the Brothers of Charity Early Intervention Services in County Galway, a service that caters for children under 6 years with learning disabilities. The aim in doing this study was to assess the value of routine developmental screening in identifying children with learning difficulties. This study also investigates the patterns and sources of referral to the remedial services provided by the Brothers of Charity and highlights possible avoidable delays in referral. The results showed that many children were referred for remedial services late. The reasons for late referral included late identification of some children with problems, insufficient co-ordination of community-based services and a lack of awareness of the importance of early intervention in some cases. As some communication disorders such as autism, autistic spectrum disorders and specific language delay may not express themselves until the later part of the second year of life, the 18-24 month developmental assessment is of vital importance. However identification of these disorders can present difficulties and may call for additional training for professionals involved in the developmental screening of children in that age group. The interval between initial identification and referral for remedial care in many cases was more than twelve months. We propose that, in order to minimize this time, children requiring a more in-depth assessment should be assessed by a community-based multidisciplinary team, enabling integrated assessment by the different disciplines and thus speedier referral to remedial services.

6.74. Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A., Courchesne, R.Y. "Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study." *Neurology* 2001 Jul 24;57(2):245-54.

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OBJECTIVE: To quantify developmental abnormalities in cerebral and cerebellar volume in autism. **METHODS:** The authors studied 60 autistic and 52 normal boys (age, 2 to 16 years) using MRI. Thirty autistic boys were diagnosed and scanned when 5 years or older. The other 30 were scanned when 2 through 4 years of age and then diagnosed with autism at least 2.5 years later, at an age when the diagnosis of autism is more reliable. **RESULTS:** Neonatal head circumferences from clinical records were available for 14 of 15 autistic 2- to 5-year-olds and, on average, were normal (35.1 +/- 1.3 cm versus clinical norms: 34.6 +/- 1.6 cm), indicative of normal overall brain volume at birth; one measure was above the 95th percentile. By ages 2 to 4 years, 90% of autistic boys had a brain volume larger than normal average, and 37% met criteria for developmental macrocephaly. Autistic 2- to 3-year-olds had more cerebral (18%) and cerebellar (39%) white matter, and more cerebral cortical gray matter (12%) than normal, whereas older autistic children and adolescents did not have such enlarged gray and white matter volumes. In the cerebellum, autistic boys had less gray matter, smaller ratio of gray to white matter, and smaller vermis lobules VI-VII than normal controls. **CONCLUSIONS:** Abnormal regulation of brain growth in autism results in early overgrowth followed by abnormally slowed growth. Hyperplasia was present in cerebral gray matter and cerebral and cerebellar white matter in early life in patients with autism.

6.75. Hisaoka, S., Harada, M., Nishitani, H., Mori, K. "Regional magnetic resonance spectroscopy of the brain in autistic individuals." *Neuroradiology* 2001 Jun;43(6):496-8.

Department of Radiology, School of Medicine, University of Tokushima, Japan.

We studied the variations in the concentration of metabolites with brain region and age in autistic individuals and normal controls using multiple analysis of covariance. We examined 55 autistic individuals (2-21 years old, 47 male and eight female) and 51 normal children (3 months-15 years old, 26 boys and 25 girls). Single volumes of interest were placed in the frontal, parietal and temporal region on both sides, the brain stem and cingulate gyrus. The concentration of each metabolite was quantified by the water reference method. The concentration of N-acetylaspartate in the temporal regions (Brodmann's areas 41 and 42) in the autistic individuals were significantly lower than those in the controls ($P < 0.05$), but concentrations in other regions were not significantly different between the autistic individuals and controls. This suggests low density or dysfunction of neurones in Brodmann's areas 41 and 42 in autistic individual, which might be related to the disturbances of the sensory speech centre (Wernicke's area) in autism.

6.76. Charman, T., Baron-Cohen, I., Baird, G., Cox, A., Wheelwright, S., Swettenham, J., Drew, A. "Commentary: The Modified Checklist for Autism in Toddlers." *J Autism Dev Disord* 2001 Apr;31(2):145-8; discussion 149-51. Publication Types: Comment.

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The question of when it is best to screen for autism may only be answered by a series of empirical studies. These will be difficult to plan, fund, and conduct, and will by necessity take many years because of the need to systematically follow up the whole cohort screened. In our study, we identified 19 of the 50 children with autism by their profile at the 18-month screen (though note that some fell out of risk status at the repeat screen 1 month later—thus sacrificing sensitivity for improved positive predictive power). Through the subsequent surveillance methods we employed, we identified the remaining cases as follows: 5 at 42 months, 4 between 42 months and 7 years, and 25 at 7 years. We do not mean to end on a pessimistic note. Our experiences have been positive both in regard to the instrument we developed and the effects that using it have had on the health practitioners involved in the research study. In discussion, practitioners have commented on the usefulness of knowing what prelanguage and prosocial skills can reliably be looked at during the 18-month check. Training using the CHAT and eliciting its behaviors improved the skills and confidence of primary health practitioners. It is our view that this has had the effect of reducing the age at which autism is recognized and cases are referred on for a developmental assessment. The work reported by Robins et al. makes an important contribution to this ongoing research and clinical process as we attempt to accurately identify children with autism at a young age.

6.77. Robins, D.I., Fein, D., Barton, M.L., Green, J.A. "The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders." *J Autism Dev Disord* 2001 Apr;31(2):131-44. Publication Types: Validation Studies.

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Autism, a severe disorder of development, is difficult to detect in very young children. However, children who receive early intervention have improved long-term prognoses. The Modified Checklist for Autism in Toddlers (M-CHAT), consisting of 23 yes/no items, was used to screen 1,293 children. Of the 58 children given a diagnostic/developmental evaluation, 39 were diagnosed with a disorder on the autism spectrum. Six items pertaining to social relatedness and communication were found to have the best discriminability between children diagnosed with and without autism/PDD. Cutoff scores were created for the best items and the total checklist. Results indicate that the M-CHAT is a promising instrument for the early detection of autism.

6.78. Mayes, S.D., Calhoun, S.L., Crites, D.L. "Does DSM-IV Asperger's disorder exist?" *J Abnorm Child Psychol* 2001 Jun;29(3):263-71.

Department of Psychiatry, The Pennsylvania State University College of Medicine, Hershey, USA.

DSM-IV criteria for autistic and Asperger's disorders were applied to 157 children with clinical diagnoses of autism or Asperger's disorder. All children met the DSM-IV criteria for autistic disorder and none met criteria for Asperger's disorder, including those with normal intelligence and absence of early speech delay. The reason for this was that all children had social impairment and restricted and repetitive behavior and interests (required DSM-IV symptoms for both autistic and Asperger's disorders) and all had a DSM-IV communication impairment (which then qualified them for a diagnosis of autistic disorder and not Asperger's disorder). Communication problems exhibited by all children were impaired conversational speech or repetitive, stereotyped, or idiosyncratic speech (or both), which are DSM-IV criteria for autism. These findings are consistent with those of 5 other studies and indicate that a DSM-IV diagnosis of Asperger's disorder is unlikely or impossible.

6.79. Saitoh, O., Karns, C.M., Courchesne, E. "Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism." *Brain* 2001 Jul;124(Pt 7):1317-24. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Psychiatry, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan.

Autism, a neuropsychiatric disorder that severely impairs social, language and cognitive development, has a clinical onset in the first years of life. Because components of the limbic system mediate memory, social and affective functions that are typically disturbed in autism, a developmental defect in the limbic system has been hypothesized to underlie different autistic symptoms, but no developmental study has been performed. To obtain neuroanatomical evidence of limbic system abnormality in autism, we measured the cross-sectional area of the area dentata (AD; dentate gyrus + CA4) and combined area of the subiculum and CA1-CA3 (CAS) using in vivo MRI. Autistic patients aged 29 months to 42 years (n = 59) and healthy normal controls (n = 51) participated. The cross-sectional area of the AD was significantly smaller than normal in autism, the largest deviation from normal size (-13.5%) being found in autistic children aged 29 months to 4 years. Strong age-related increases were seen in the cross-sectional area of CAS, but autistic and normal subjects were not significantly different. This is the first direct evidence that anatomical abnormality within the limbic system exists from the earliest years of the disorder, and persists throughout development and to middle age.

6.80. Baird, G., Charman, T., Santosh, P.J. "Clinical considerations in the diagnosis of autism spectrum disorders." *Indian J Pediatr* 2001 May;68(5):439-49.

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The diagnosis of autistic spectrum disorders (ASD) is being made more frequently in children and at younger ages. This

paper discusses various factors to be considered in the screening of autism, early features of presentation, relevant to assessment and diagnosis, subtypes or different syndromes within the spectrum of autistic conditions including Asperger syndrome, the differential diagnosis from learning and language disorders and the medical and behavioural commonly associated disorders.

6.81. Nylander, L., Gillberg, C. "Screening for autism spectrum disorders in adult psychiatric out-patients: a preliminary report." *Acta Psychiatr Scand* 2001 Jun;103(6):428-34. Publication Types: Evaluation Studies.

Department of Psychiatry, Lund University, Sweden.

OBJECTIVE: To estimate the prevalence of autism spectrum disorders (ASD) among adult psychiatric out-patients; to evaluate the efficacy of a new brief screening questionnaire (ASDASQ). **Method:** 1323 adult psychiatric out-patients were screened by staff. Analysis of psychiatric records of patients (n = 66) scoring high on the ASDASQ yielded 31 patients with a suspected ASD. Twenty-two of these patients were clinically examined. Three psychometric aspects of the questionnaire were studied. **RESULTS:** Seventeen patients were found by clinical examination to have an ASD. Since two patients scoring low on the ASDASQ were known to have an ASD, at least 19 patients in this population (1.4%) had a definite ASD. Seventeen of the ASD patients had been previously diagnosed with other psychiatric disorders, most frequently schizophrenia (n = 5). Of patients attending a treatment centre for severe psychiatric disabilities (n = 499), 3.2% had an ASD. The ASDASQ showed good reliability across and within raters. Internal consistency was excellent. **CONCLUSION:** Adult psychiatric patients sometimes have undiagnosed autism spectrum disorders. The ASDASQ can be useful for screening.

6.82. Hardan, A.Y., Minshew, N.J., Harenski, K., Keshavan, M.S. "Posterior fossa magnetic resonance imaging in autism." *J Am Acad Child Adolesc Psychiatry* 2001 Jun;40(6):666-72.

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OBJECTIVE: To determine whether the sizes and volumes of the posterior fossa structures are abnormal in non-mentally retarded autistic adolescents and adults. **METHOD:** Volume measurements of the cerebellum, vermis, and brainstem were obtained from coronal magnetic resonance imaging scans in 16 autistic subjects and 19 group-matched healthy controls. For the purpose of comparison with previous studies, area measurements of the midbrain, pons, medulla, total cerebellar vermis, and its three subregions were also obtained from a larger sample of 22 autistic males (mean age: 22.4 years; range: 12.2-51.8 years) and 22 individually matched controls (mean age 22.4 years; range: 12.9-52.2 years). **RESULTS:** The total volume of the cerebellum and the cerebellar hemispheres were significantly larger: in the autistic subjects with and without

correcting for total brain volume. Volumes of the vermis and the brainstem and all area measurements did not differ significantly between groups. **CONCLUSIONS:** There is an increase in the volume of the cerebellum in people with autism consistent with the increase in regional and total brain size reported in this developmental disorder. This finding is also concordant with evidence of cerebellar abnormalities from neuropathological and neuropsychological studies that point to the role of this structure, as part of a complex neural system, in the pathophysiology of autism.

6.83. Ravizza, S.M., Ivry, R.B. "Comparison of the basal ganglia and cerebellum in shifting attention." *J Cogn Neurosci* 2001 Apr 1;13(3):285-97.

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The basal ganglia and cerebellum have traditionally been associated with motor performance. Recently, there has been considerable interest regarding the contributions of these subcortical structures to aspects of cognition. In particular, both the basal ganglia and cerebellum have been hypothesized to be involved in the control of attentional set. To date, no neuropsychological studies have directly compared the effects of basal ganglia and cerebellar dysfunction on the same attention shifting tasks. To this end, we employed an alternating attention task that has been used to demonstrate putative attentional control deficits in children with cerebellar pathology, either related to autism or neurological insult. When adult patients with either Parkinson's disease or cerebellar lesions were tested on this task, a similar pattern of deficits was observed for both groups. However, when the motor demands were reduced, cerebellar patients showed a significant improvement on the alternating attention task, whereas the Parkinson patients continued to exhibit an impairment. This dissociation suggests that attentional deficits reported previously as being due to cerebellar dysfunction may be, at least in part, secondary to problems related to coordinating successive responses. In contrast, attention-shifting deficits associated with basal ganglia impairment cannot be explained by recourse to the motor demands of the task.

6.84. Committee on Children With Disabilities. "Technical report: the pediatrician's role in the diagnosis and management of autistic spectrum disorder in children." *Pediatrics* 2001 May;107(5):E85. Publication Types: Technical Report.

Autism and its milder variants are not rare. Most pediatricians will have the opportunity to provide a medical home for a child with autism. This technical report serves to complement and expand on the information in the accompanying policy statement to increase the pediatrician's fund of knowledge and comfort level in caring for children with autism. In so doing, it is anticipated that earlier diagnosis and referral for appropriate intervention will be possible and that this will, in turn, have a positive effect on long-term outcomes for children with autism and their families.

6.85. Committee on Children With Disabilities. "American Academy of Pediatrics: The pediatrician's role in the diagnosis and management of autistic spectrum disorder in children." *Pediatrics* 2001 May;107(5):1221-6. Publication Types: Guideline, Practice Guideline.

Primary care physicians have the opportunity, especially within the context of the medical home, to be the first point of contact when parents have concerns about their child's development or behavior. The goal of this policy statement is to help the pediatrician recognize the early symptoms of autism and participate in its diagnosis and management. This statement and the accompanying technical report will serve to familiarize the pediatrician with currently accepted criteria defining the spectrum of autism, strategies used in making a diagnosis, and conventional and alternative interventions.

6.86. Allen, D.A., Steinberg, M., Dunn, M., Fein, D., Feinstein, C., Waterhouse, L., Rapin, I. "Autistic disorder versus other pervasive developmental disorders in young children: same or different?" *Eur Child Adolesc Psychiatry* 2001 Mar;10(1):67-78.

Division of Child Psychiatry, Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA.

Eighteen preschool children diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised (DSM III-R) as having Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) were compared to 176 children with DSM III-R Autistic Disorder (AD), and to 311 non-autistic children with developmental language disorders (DLD) (N = 201) or low IQ (N = 110). All children were partitioned into "high" and "low" cognitive subgroups at a nonverbal IQ of 80. Within cognitive subgroups, the 18 PDD-NOS children did not differ significantly from either the DLD or the AD children in verbal and adaptive skills and obtained scores intermediate between those of these groups. The PDD-NOS did not differ from the AD children in maladaptive behaviors. Both the PDD-NOS and AD children had many more of these behaviors than the non-autistic comparison groups. Children in the "high" and "low" cognitive subgroups of AD, but not of PDD-NOS, differed substantially on most measures, with the children with lower cognitive scores significantly more impaired on all measures. Similarity of PDD-NOS children to AD children in maladaptive behaviors and an intermediate position between autistic and non-autistic groups on virtually all measures explains the difficulty clinicians encounter in classifying children with PDD and raises questions about the specificity of these diagnostic subtypes of the autistic spectrum.

6.87. Muller, R.A., Pierce, K., Ambrose, J.B., Allen, G., Courchesne, E. "Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study." *Biol Psychiatry* 2001 Apr 15;49(8):665-76.

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BACKGROUND: Early neurodevelopmental pathogenesis in autism potentially affects emerging functional maps, but little imaging evidence is available. **METHODS:** We studied eight male autistic and eight matched normal subjects, using functional magnetic resonance imaging during visually paced finger movement, compared to a control condition (visual stimulation in the absence of motor response). **RESULTS:** Groupwise analyses showed activation in contralateral perirolandic cortex, basal ganglia, and thalamus, bilateral supplementary motor area, and ipsilateral cerebellum for both groups. However, activations were less pronounced in the autism group. Direct group comparisons demonstrated greater activation in perirolandic and supplementary motor areas in the control group and greater activation (or reduced deactivation) in posterior and prefrontal cortices in the autism group. Intraindividual analyses further showed that strongest activations were consistently located along the contralateral central sulcus in control subjects but occurred in locations differing from individual to individual in the autism group. **CONCLUSIONS:** Our findings, though based on a rather small sample, suggest abnormal individual variability of functional maps and less distinct regional activation/deactivation patterns in autism. The observations may relate to known motor impairments in autism and are compatible with the general hypothesis of disturbances of functional differentiation in the autistic cerebrum.

6.88. Townsend, J., Westerfield, M., Leaver, E., Makeig, S., Jung, T., Pierce, K., Courchesne, E. "Event-related brain response abnormalities in autism: evidence for impaired cerebello-frontal spatial attention networks." *Brain Res Cogn Brain Res* 2001 Mar;11(1):127-45. Publication Types: Clinical Trial, Controlled Clinical Trial.

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Although under some conditions the attention-related late positive event-related potential (ERP) response (LPC) is apparently normal in autism during visual processing, the LPC elicited by visuospatial processing may be compromised. Results from this study provide evidence for abnormalities in autism in two components of the LPC generated during spatial processing. The early frontal distribution of the LPC which may reflect attention orienting was delayed or missing in autistic subjects during conditions in which attention was to peripheral visual fields. The later parietal distribution of the LPC which may be associated with context updating was smaller in amplitude in autistic subjects regardless of attention location. Both abnormalities suggest disruption of function in spatial attention networks in autism. Evidence that the cerebellar abnormalities in autism may underlie these deficits comes from: (1) similar results in ERP responses and spatial attention deficits in patients with cerebellar lesions; (2) brain-behavior correlations in normally functioning individuals associating the size of the posterior cerebellar vermis and the latency of the frontal LPC; and (3) a previously reported complementary correlation between the size of the posterior vermal lobules and spatial orienting speed. Although the scalp-recorded LPC is thought to be cortically generated, it

may be modulated by subcortical neural activity. The cerebellum may serve as a modulating influence by affecting the task-related antecedent attentional process. The electrophysiological abnormalities reported here index spatial attention deficits in autism that may reflect cerebellar influence on both frontal and parietal spatial attention function.

6.89. Noterdaeme, M., Sitter, S., Mildenberger, K., Amorosa, H. "Diagnostic assessment of communicative and interactive behaviours in children with autism and receptive language disorder." *Eur Child Adolesc Psychiatry* 2000 Dec;9(4):295-300. Publication Types: Validation Studies.

Heckscher Klinik für Kinder- und Jugendpsychiatrie, München.

Children with autism and children with a severe specific receptive language disorder both show clear deficits in communicative language skills and in social relationships. In this study the usefulness of the Autism Diagnostic Observation Schedule (ADOS) in the differential diagnosis between these two groups of developmentally impaired children is assessed. 11 children with early infantile autism and 20 children with a specific receptive language disorder participated in the study. 18 children with an expressive language disorder were used as a control group. The ADOS was individually administered to all children by the same examiner. The results showed that on most of the ADOS measures the autistic children were clearly more deviant than the language impaired children. There were no significant differences between the two groups of language impaired children. Eight out of 11 autistic children reached the defined cut-off values on the measures "language and communication" and "social interaction" of the ADOS algorithm, whereas only three autistic children did so on the measure "stereotyped behaviour". None of the language-impaired children reached the cut-off values on more than one measure. The ADOS allowed for good assessment of certain types of behaviour. However, to confirm the diagnosis of infantile autism, additional information from parents is required.

6.90. Hashimoto, T., Sasaki, M., Fukumizu, M., Hanaoka, S., Sugai, K., Matsuda, H. "Single-photon emission computed tomography of the brain in autism: effect of the developmental level." *Pediatr Neurol* 2000 Nov;23(5):416-20.

Department of Education for Handicapped Children, Naruto University of Education, 748, Nakashima, Takashima, Narutocho, Naruto-city, Tokushima, Japan.

Brain single-photon emission computed tomography was performed in 22 autistic and 10 nonautistic disabled patients. The regional cerebral blood flow in both laterotemporal and dorso-medio-lateral frontal areas decreased significantly in the autistic group compared with in nonautistic group. In the autistic group, the regional cerebral blood flow was significantly higher in the right temporal and right parietal lobes than that in the left ones. Inversely, the regional cerebral blood flow in the frontal and occipital lobes was significantly higher on the left side than on the right side. In the nonautistic group, except for in the dorso-medio-lateral frontal lobes (left

> right), there was no difference in the regional cerebral blood flow in either cerebrum or cerebellum. A positive correlation between regional cerebral flow and development quotient (intelligence quotient) was observed in the left laterotemporal and both dorso-medio-lateral frontal areas, and a negative one was observed in the cerebellar vermis area. These results suggest that the regional cerebral blood flow decrease in the temporal and frontal areas relates to not only the brain mechanism of autism reported previously but also intelligence levels.

6.91. Ballaban-Gil, K., Tuchman, R. "Epilepsy and epileptiform EEG: association with autism and language disorders." *Ment Retard Dev Disabil Res Rev* 2000;6(4):300-8. Publication Types: Review, Review, Tutorial.

Departments of Neurology and Pediatrics and the Montefiore/AECOM Epilepsy Management Unit, Albert Einstein College of Medicine, Bronx, New York, USA.

The relationship between epilepsy, language, behavior, and cognition is not well understood. Developmental and acquired disabilities such as autistic spectrum disorders, Landau-Kleffner Syndrome, electrical status epilepticus in sleep, and developmental dysphasias have been associated with epileptiform abnormalities. These disorders share many common features and raise important questions regarding this intricate relationship. This article reviews these disorders and discusses the proposed interaction between epileptiform abnormalities and cognitive dysfunction. Diagnostic and treatment issues will also be reviewed.

6.92. Haznedar, M.M., Buchsbaum, M.S., Wei, T.C., Hof, P.R., Cartwright, C., Bienstock, C.A., Hollander, E. "Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging." *Am J Psychiatry* 2000 Dec;157(12):1994-2001.

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OBJECTIVE: Cytoarchitectonic changes in the anterior cingulate cortex, hippocampus, subiculum, entorhinal cortex, amygdala, mammillary bodies, and septum were reported in a postmortem study of autism. Previously, the authors found smaller cingulate volume and decreased metabolism of the cingulate in seven autistic patients. In this study, they measured the volume and glucose metabolism of the amygdala, hippocampus, and cingulate gyrus in an expanded group of 17 patients with autism spectrum disorders (autism [N=10] or Asperger's disorder [N=7]) and 17 age- and sex-matched healthy volunteers. **METHOD:** Subjects performed a serial verbal learning test during (18)F-deoxyglucose uptake. The amygdala, hippocampus, and cingulate gyrus were outlined on magnetic resonance imaging scans, volumes of the structures were applied to matching coregistered positron emission tomography scans, and three-dimensional significance probability mapping was performed. **RESULTS:** Significant metabolic reductions in both the anterior and posterior cingulate gyri were visualized in the patients with

autism spectrum disorders. Both Asperger's and autism patients had relative glucose hypometabolism in the anterior and posterior cingulate as confirmed by analysis of variance; regional differences were also found with three-dimensional significance probability mapping. No group differences were found in either the metabolism or the volume of the amygdala or the hippocampus. However, patients with autism spectrum disorders showed reduced volume of the right anterior cingulate gyrus, specifically in Brodmann's area 24'. **CONCLUSIONS:** Compared with age- and sex-matched healthy volunteers, patients with autism spectrum disorders showed significantly decreased metabolism in both the anterior and posterior cingulate gyri.

6.93. Zilbovicius, M., Boddart, N., Belin, P., Poline, J.B., Remy, P., Mangin, J.F., Thivard, L., Barthelemy, C., Samson, Y. "Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography." *Am J Psychiatry* 2000 Dec;157(12):1988-93.

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OBJECTIVE: The nature of the underlying brain dysfunction of childhood autism, a life-long severe developmental disorder, is not well understood. Although researchers using functional brain imaging have attempted to contribute to this debate, previous studies have failed to report consistent localized neocortical brain dysfunction. The authors reasoned that early methods may have been insensitive to such dysfunction, which may now be detectable with improved technology. **METHOD:** To test this hypothesis, regional cerebral blood flow was measured with positron emission tomography (PET) in 21 children with primary autism and in 10 nonautistic children with idiopathic mental retardation. Autistic and comparison groups were similar in average age and developmental quotients. The authors first searched for focal brain dysfunction in the autistic group by using a voxel-based whole brain analysis and then assessed the sensitivity of the method to detect the abnormality in individual children. An extension study was then performed in an additional group of 12 autistic children. **RESULTS:** The first autistic group had a highly significant hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex, which was detected in 76% of autistic children. Virtually identical results were found in the second autistic group in the extension study. **CONCLUSIONS:** PET and voxel-based image analysis revealed a localized dysfunction of the temporal lobes in school-aged children with idiopathic autism. Further studies will clarify the relationships between these temporal abnormalities and the perceptive, cognitive, and emotional developmental abnormalities characteristic of this disorder.

6.94. Maziade, M., Merette, C., Cayer, M., Roy, M.A., Szatmari, P., Cote, R., Thivierge, J. "Prolongation of brainstem auditory-evoked responses in autistic probands and their unaffected relatives." *Arch Gen Psychiatry* 2000 Nov;57(11):1077-83.

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BACKGROUND: Brain function, as indexed by brain electrical activity, is heritable in humans, and it may be impaired in autism. Autism also has strong genetic determinants, and like all major psychiatric disorders, its complex clinical phenotype renders genetic studies difficult. Innovative strategies focused on alternative biological phenotypes are needed. **METHODS:** The early brain auditory-evoked response was assessed in 73 autistic probands and 251 relatives who were compared with 521 normal controls. **RESULTS:** We first confirmed in the autistic probands the presence of a slowing in nerve conduction in the auditory system as expressed by the prolongation of early brain auditory-evoked response under the form of I-III interpeak latencies (IPLs). Furthermore, we observed the same I-III IPL prolongation in the unaffected first degree relatives of the autistic probands compared with controls. Despite clear evidence of a coaggregation of autism and I-III IPL prolongation in families, the IPLs did not seem to be the sole liability factor for autism as suggested by the observation of 52% of families in which the autistic proband and relatives showed normal IPLs. **CONCLUSION:** A prolongation of the early brain auditory-evoked response IPLs may be a marker for one of several deficits underlying autism and deserves further analysis as a potential alternative phenotype for the disorder.

6.95. Lord, C., Risi, S., Lambrecht, L., Cook, E.H. Jr., Leventhal, B.L., DiLavore, P.C., Pickles, A., Rutter, M. "The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism." *J Autism Dev Disord* 2000 Jun;30(3):205-23.

University of Chicago, Illinois, USA.

The Autism Diagnostic Observation Schedule-Generic (ADOS-G) is a semistructured, standardized assessment of social interaction, communication, play, and imaginative use of materials for individuals suspected of having autism spectrum disorders. The observational schedule consists of four 30-minute modules, each designed to be administered to different individuals according to their level of expressive language. Psychometric data are presented for 223 children and adults with Autistic Disorder (autism), Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) or nonspectrum diagnoses. Within each module, diagnostic groups were equivalent on expressive language level. Results indicate substantial interrater and test-retest reliability for individual items, excellent interrater reliability within domains and excellent internal consistency. Comparisons of means indicated consistent differentiation of autism and PDDNOS from nonspectrum individuals, with some, but less consistent, differentiation of autism from PDDNOS. A priori operationalization of DSM-IV/ICD-10 criteria, factor analyses, and ROC curves were used to generate diagnostic algorithms with thresholds set for autism and broader autism spectrum/

PDD. Algorithm sensitivities and specificities for autism and PDDNOS relative to nonspectrum disorders were excellent, with moderate differentiation of autism from PDDNOS.

6.96. Carr, J.E., Nicolson, A.C., Higbee, T.S. "Evaluation of a brief multiple-stimulus preference assessment in a naturalistic context." *J Appl Behav Anal* 2000 Fall;33(3):353-7.

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We evaluated a brief multiple-stimulus preference assessment within the context of an early intervention program for 3 children who had been diagnosed with autism. Subsequent curriculum-based reinforcer evaluations confirmed the predictions of the preference assessments. In addition, eight additional preference assessments that were conducted over a period of 1 month indicated generally stable preferences for 2 of the 3 participants.

6.97. Gillham, J.E., Carter, A.S., Volkmar, F.R., Sparrow, S.S. "Toward a developmental operational definition of autism." *J Autism Dev Disord* 2000 Aug;30(4):269-78.

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Traditional approaches to diagnosing autism emphasize delays in communication and socialization. Traditional diagnostic schemes typically list symptoms (e.g., lack of eye contact), but provide little guidance on how to incorporate information about developmental level in making a diagnosis. Because standardized measures of adaptive behavior can provide information about children's communication, socialization, and other behavior relative to their age, they may be useful tools for diagnosing autism. This study investigated the ability of the Vineland Adaptive Behavior Scales to identify children with autism. Vineland scores and measures of intellectual functioning were obtained for children with autism, PDDNOS, and other developmental disorders (DD). Discriminant function analyses indicated that the autism and combined nonautism (PDDNOS and DD) groups could be differentiated on the basis of socialization, daily living skills, and serious maladaptive behaviors. Socialization alone accounted for 48% of the variance in diagnosis. Using regression analyses derived from a large normative sample, adaptive behavior scores were predicted from chronological age (CA) and mental age (MA). Socialization scores in the autism group were substantially below the level predicted from CA or MA. An index derived from the ratio of actual to predicted socialization scores correctly classified 86% of both autism and nonautism cases. Findings suggest that comparison of obtained Vineland socialization scores to those predicted by CA or MA may be useful in clarifying the diagnosis of autism.

6.98. Eliez, S., Reiss, A.L. "MRI neuroimaging of childhood psychiatric disorders: a selective review." *J Child Psychol Psychiatry* 2000 Sep;41(6):679-94.

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Over the past 10 years, innovations in physics and computer science have promoted magnetic resonance imaging (MRI) as an essential tool for investigating the biological substrates of psychiatric disorders. Requiring no radiation exposure, MRI is now the preferred imaging technique for pediatric populations. However, the rapid technical advances in MRI pulse sequences, data processing, and analysis have made it increasingly complex for clinicians to compare and critically evaluate MRI research studies. This paper selectively reviews MRI research on five psychiatric conditions occurring in childhood or adolescence: ADHD, autism, childhood-onset schizophrenia, Tourette syndrome, and early-onset depression. The selection of papers reviewed was based on four criteria: the originality of the idea underlying the paper, the quality of the sample and methodologies used, the presence of controversial findings in the paper, and whether the paper was a clear illustration of specific methodological strengths or weaknesses. The two goals of this review paper are to update clinicians on morphometric brain imaging in child psychiatry and the methodological issues pertaining to image acquisition and analysis, and to promote critical reading of future MRI studies.

6.99. Baron-Cohen, S. "Is asperger syndrome/high-functioning autism necessarily a disability?" *Dev Psychopathol* 2000 Summer;12(3):489-500. Publication Types: Review, Review, Tutorial.

Department of Experimental Psychology, University of Cambridge, UK.

This article considers whether Asperger syndrome (AS) or high-functioning autism (HFA) necessarily leads to disability or whether AS/HFA simply leads to "difference." It concludes that the term "difference" in relation to AS/ HFA is a more neutral, value-free, and fairer description than terms such as "impairment," "deficiency," or "disability"; that the term "disability" only applies to the lower functioning cases of autism; but that the term "disability" may need to be retained for AS/HFA as long as the legal framework provides financial and other support only for individuals with a disability. Two models are summarized which attempt to define in what way individuals with AS/HFA are "different": the central coherence model, and the folk psychology-folk physics model. The challenge for research is to test the value of such models and to precisely characterize the differences in cognitive style.

6.100. Avdi, E., Griffin, C., Brough, S. "Parents' constructions of professional knowledge, expertise and authority during assessment and diagnosis of their child for an autistic spectrum disorder." *Br J Med Psychol* 2000 Sep;73 (Pt 3):327-38.

School of Psychology, University of Birmingham, Edgbaston, UK.

This paper presents a discourse analysis of parents' talk about the knowledge, expertise and authority of professionals, during assessment and diagnosis of their child for an autistic spectrum disorder at a Child Development Centre. Focusing

on the positional level of analysis, it was suggested that parents' constructions of professional expertise and authority were inherently ambivalent and at times contradictory. It was further argued that this ambivalence is also reflected in an ideological dilemma between equality and expertise, regarding the role and positioning of 'human relations experts'. Discourse analysis was found to be a particularly useful tool in investigating aspects of the parents' talk relating to authority, knowledge and expertise. It is suggested that acknowledging this ambivalence and scrutinizing one's assumptions and practice, rather than denying the authoritarian aspects of health care, would provide the basis for more ethical and respectful clinical practice.

6.101. Rumsey, J.M., Ernst, M. "Functional neuroimaging of autistic disorders." *Ment Retard Dev Disabil Res Rev* 2000;6(3):171-9. Publication Types: Review, Review, Tutorial.

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Functional neuroimaging methods hold promise for elucidating the neurobiology of autistic disorders, yet they present difficult practical and scientific challenges when applied to these complex and heterogeneous syndromes. Single-state studies of brain metabolism and blood flow thus far have failed to yield consistent findings, but suggest considerable variability in regional patterns of cerebral synaptic activity. Patients with idiopathic autism are less likely to show abnormalities than are patients with comorbid illness or epilepsy. Activation studies have begun to suggest alterations in brain organization for language and cognition. Neurotransmitter studies using positron emission tomography (PET) suggest abnormalities of serotonergic and dopaminergic function. Studies using magnetic resonance spectroscopy (MRS) have begun to document metabolic deficits in the frontal cortex and cerebellum. A single study using magnetoencephalography suggests a high incidence of epileptiform activity in children with autistic regression. Research needs include well-controlled developmental studies, particularly of young subjects and relatively homogeneous subgroups, which balance scientific rigor with ethical constraints. Investigations of the serotonergic and dopaminergic systems, limbic-based memory and emotional systems, and the role of epileptiform activity in autism represent priorities for future research.

6.102. Davidson, R.J., Slagter, H.A. "Probing emotion in the developing brain: functional neuroimaging in the assessment of the neural substrates of emotion in normal and disordered children and adolescents." *Ment Retard Dev Disabil Res Rev* 2000;6(3):166-70. Publication Types: Review, Review, Tutorial.

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Virtually all developmental neuropsychiatric disorders involve some dysfunction or dysregulation of emotion. Moreover, many psychiatric disorders with adult onset have early subclinical manifestations in children. This essay selectively reviews the literature on the neuroimaging of affect and disorders of affect in children. Some critical definitional and conceptual issues are first addressed, including the distinctions between the perception and production of emotion and between emotional states and traits. Developmental changes in morphometric measures of brain structure are then discussed and the implications of such findings for studies of functional brain activity are considered. Data on functional neuroimaging and childhood depression are then reviewed. While the extant data in this area are meager, they are consistent with studies in adults that have observed decreased left-sided anterolateral prefrontal cortex activation in depression. Studies in children on the recognition of emotion and affective intent in faces using functional magnetic resonance imaging are then reviewed. These findings indicate that the amygdala plays an important role in such affective face processing in children, similar to the patterns of activation observed in adults. Moreover, one study has reported abnormalities in amygdala activation during a task requiring the judgment of affective intent from the eye region of the face in subjects with autism. Some of the methodological complexities of developmental research in this area are discussed, and directions for future research are suggested.

6.103. Ward, P.E. "Potential diagnostic aids for abnormal fatty acid metabolism in a range of neurodevelopmental disorders." *Prostaglandins Leukot Essent Fatty Acids* 2000 Jul-Aug;63(1-2):65-8. Publication Types: Review, Review, Tutorial.

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Disorders of neurodevelopment include attention deficit hyperactivity disorder, dyspraxia, dyslexia and autism. There is considerable co-morbidity of these disorders and their identification often presents difficulties to those making a diagnosis. This is especially difficult when a multidisciplinary approach is not adopted. All of these disorders have been reported as associated with fatty acid abnormalities ranging from genetic abnormalities in the enzymes involved in phospholipid metabolism to symptoms reportedly improved following dietary supplementation with long chain fatty acids. If definitive disorders of lipid metabolism could be defined then the diagnosis and subsequent management of neurodevelopmental disorders might be transformed. In the identification of those disorders of development which involve lipid metabolism, there are now several tests, measures of lipid metabolism, which could be useful. Copyright 2000 Harcourt Publishers Ltd.

6.104. Jones, G.S. "Autistic spectrum disorder: diagnostic difficulties." *Prostaglandins Leukot Essent Fatty Acids* 2000 Jul-Aug;63(1-2):33-6. Publication Types: Review, Review, Tutorial.

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Recognition of the autistic spectrum disorders is becoming more widespread amongst basic scientists, clinicians, and the general population. The term does not imply anything about pathology or aetiology, although it has proved to be a useful concept clinically. From Kanner's classical autism the concept has widened in scope to include milder and more subtle impairments. From a clinical perspective, there are many alternative diagnoses in an individual with autistic-like symptoms, and thorough investigation is necessary to exclude these. Copyright 2000 Harcourt Publishers Ltd.

6.105. Elia, M., Ferri, R., Musumeci, S.A., Panerai, S., Bottitta, M., Scuderi, C. "Clinical correlates of brain morphometric features of subjects with low-functioning autistic disorder." *J Child Neurol* 2000 Aug;15(8):504-8.

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Numerous neuropathologic and imaging studies have reported different structural abnormalities in the brains of autistic subjects. However, whether or not the degree of brain abnormality is correlated with the severity of developmental impairment in autistic disorder is still unknown. The midsagittal area of the cerebrum, corpus callosum, midbrain, cerebellar vermis, and vermal lobules VI and VII was measured by means of magnetic resonance imaging in 22 boys with low-functioning autistic disorder and in 11 age-matched normal controls. Morphometric measures were statistically compared between groups and correlated with age and scores on the Psychoeducational Profile-Revised and the Childhood Autism Rating Scale. A significant negative correlation was found between-midsagittal area of the cerebrum and age in patients with autistic disorder, and a positive correlation was found between the midsagittal area of the midbrain and some subscales of the Psychoeducational Profile-Revised.

6.106. Starkstein, S.E., Vazquez, S., Vrancic, D., Nanclares, V., Manes, F., Piven, J., Plebst, C. "SPECT findings in mentally retarded autistic individuals." *J Neuropsychiatry Clin Neurosci* 2000.

Division of Child Psychiatry, Department of Neuropsychiatry, Raul Carrea Institute of Neurological Research, Buenos Aires, Argentina. ses@fleni.org.ar

The authors examined specific deficits of cerebral blood perfusion in autistic patients as measured with [(99m)Tc]HMPAO single-photon emission computed tomography (SPECT). The study, conducted in an outpatient clinic setting, included a consecutive series of 30 patients with autism and 14 patients with mental retardation but no autism comparable in chronological age, mental age, height, weight, and head circumference. All participants were examined with a comprehensive psychiatric and neuropsychological battery and received a [(99m)Tc]HMPAO SPECT scan. Autistic patients had significantly lower perfusion than the control group in the following brain regions: right temporal lobe (basal and inferior areas), occipital lobes, thalami, and left basal ganglia. The study demonstrated significant perfusion deficits

in specific brain areas of moderately to severely mentally retarded autistic patients.

6.107. Filipek, P.A., Accardo, P.J., Ashwal, S., Baranek, G.T., Cook, E.H. Jr., Dawson, G., Gordon, B., Gravel, J.S., Johnson, C.P., Kallen, R.J., Levy, S.E., Minshew, N.J., Ozonoff, S., Prizant, B.M., Rapin, I., Rogers, S.J., Stone, W.L., Teplin, S.W., Tuchman, R.F., Volkmar, F.R. "Practice parameter: screening and diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society." *Neurology* 2000 Aug 22;55(4):468-79. Publication Types: Guideline, Practice Guideline.

Departments of Pediatrics and Neurology, University of California, Irvine, USA.

Autism is a common disorder of childhood, affecting 1 in 500 children. Yet, it often remains unrecognized and undiagnosed until or after late preschool age because appropriate tools for routine developmental screening and screening specifically for autism have not been available. Early identification of children with autism and intensive, early intervention during the toddler and preschool years improves outcome for most young children with autism. This practice parameter reviews the available empirical evidence and gives specific recommendations for the identification of children with autism. This approach requires a dual process: 1) routine developmental surveillance and screening specifically for autism to be performed on all children to first identify those at risk for any type of atypical development, and to identify those specifically at risk for autism; and 2) to diagnose and evaluate autism, to differentiate autism from other developmental disorders.

6.108. Caviness, V.S. Jr., Makris, N., Langè, N.T., Herbert, M., Kennedy, D.N. "Advanced applications of MRI in human brain science." *Keio J Med* 2000 Jun;49(2):66-73. Publication Types: Review, Review, Tutorial.

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Magnetic resonance imaging of the brain is now generally indispensable to state of art clinical medicine. Robust, high resolution imaging systems are currently available worldwide. The availability of MRI has, in little more than a decade, revolutionized the certainty and efficiency of clinical diagnosis and management. As a dividend of this revolution, clinicians and radiologists who are expert in the many and varied applications of MRI methods are able to relate this expertise to a confident mastery of the topographic anatomy of the brain as revealed in magnetic resonance images. Whereas the yield to clinical objectives has been massive, the clinician as yet draws upon a relatively limited sampling of the potential informational harvest from this technology which in theory could further enrich both clinical concerns and those of fundamental neuroscience. Here we will review early explorations into these other offerings with the expectation that the coming decade will see them established comfortably

with current uses. We will also consider potential offerings of the extended applications of brain MRI to the characterization and insights into biological origins of certain obscure developmental disorders.

6.109. Hendren, R.L., De Backer, I., Pandina, G.J. "Review of neuroimaging studies of child and adolescent psychiatric disorders from the past 10 years." *J Am Acad Child Adolesc Psychiatry* 2000. Publication Types: Review, Review, Tutorial.

Institute for Quality, Research and Training, UMDNJ-Robert Wood Johnson, New Brunswick 08901, USA.

OBJECTIVES: To review recent neuroimaging studies of serious emotional disorders in youth and identify problems and promise of neuroimaging in clinical practice. METHOD: Published reports from refereed journals are briefly described, critiqued, and synthesized into a summary of the findings to date. RESULTS: Childhood-onset schizophrenia shows progressive ventricular enlargement, reduction in total brain and thalamus volume, changes in temporal lobe structures, and reductions in frontal metabolism. Autistic disorder is associated with cerebellar changes, greater total brain and lateral ventricle volume, and asymmetry. The prefrontal cortex and the basal ganglia are consistently reported as abnormal in attention-deficit/hyperactivity disorder. Patients with anorexia nervosa show enlarged CSF spaces and reductions in gray and white matter that are only partially reversible with weight recovery. CONCLUSIONS: Results from neuroimaging studies of childhood-onset psychiatric disorders suggest consistency in the structures found to be abnormal, but inconsistencies in the nature of these abnormalities. Although neuroimaging technology holds great promise for neurodevelopmental research, it is not yet a diagnostic instrument.

6.110. Buoni, S., Sorrentino, L., Farnetani, M.A., Pucci, L., Fois, A. "The syndrome of inv dup (15): clinical, electroencephalographic, and imaging findings." *J Child Neurol* 2000 Jun;15(6):380-5.

Institute of Clinical Pediatrics, University of Siena, Italy.

The clinical and laboratory data of four pediatric patients and one adult patient with inverted duplication (inv dup) (15) are reported. The most evident findings were dysmorphic features with frontal bossing; genital abnormalities, such as macropenis or hypospadias; mental retardation; autistic behavior; and seizures. Two additional adults with inv dup (15) from other institutions were also diagnosed in our laboratory. Seizures and mental retardation were the reasons for their referral. The clinical picture of inv dup (15) seems to be quite variable since the phenotype can also be normal. However, karyotyping and fluorescent in-situ hybridization, focused in particular on chromosome 15, appear to be indicated in patients with dysmorphic phenotypes, such as the one present in our patients, and in subjects with early-onset seizures and psychomotor retardation with autistic features.

6.111. Baird, G., Charman, T., Baron-Cohen, S., Cox, A., Swettenham, J., Wheelwright, S., Drew, A. "A screening instrument for autism at 18 months of age: a 6-year follow-up study." *J Am Acad Child Adolesc Psychiatry* 2000 Jun;39(6):694-702.

Newcomen Centre, Guy's Hospital, London.

OBJECTIVES: A population of 16,235 children aged 18 months was screened using the Checklist for Autism in Toddlers (CHAT) to identify childhood autism (CA). Two further screening procedures were conducted at age 3 and 5 years. The population was followed up at age 7 years in order to establish the sensitivity, specificity, and positive predictive value of the instrument. **METHOD:** A brief checklist assessing joint attention and pretend play behaviors was administered by primary health care practitioners when the children were 18 months old. Follow-up methods included screening through parents and health practitioners and checking medical and educational records. **RESULTS:** Nineteen cases of CA were successfully identified by the CHAT at 18 months. At follow-up a total of 50 cases of CA were identified via all surveillance methods. Thus, the CHAT has a sensitivity of 38% and a specificity of 98% for identifying CA. The positive predictive value of the instrument was maximized by concentration on the highest-risk group. Repeated screening 1 month later increased the positive predictive value to 75% for identification of CA but reduced the sensitivity to 20%, although the specificity was close to 100%. The screen also identified cases of pervasive developmental disorder as well as children with language and other developmental disorders. **CONCLUSIONS:** The CHAT can be used to identify cases of autism and related pervasive developmental disorders at 18 months of age. It is emphasized that the CHAT is not a diagnostic instrument but can identify potential cases of autism spectrum disorders for a full diagnostic assessment.

6.112. Arnold, L.E., Aman, M.G., Martin, A., Collier-Crespin, A., Vitiello, B., Tierney, E., Asarnow, R., Bell-Bradshaw, F., Freeman, B.J., Gates-Ulanet, P., Klin, A., McCracken, J.T., McDougle, C.J., McGough, J.J., Posey, D.J., Scahill, L., Swiezy, N.B., Ritz, L., Volkmar, F. "Assessment in multisite randomized clinical trials of patients with autistic disorder: the Autism RUPP Network. Research Units on Pediatric Psychopharmacology." *J Autism Dev Disord* 2000 Apr;30(2):99-111. Publication Types: Clinical Trial, Multicenter Study, Randomized Controlled Trial, Review, Review, Tutorial.

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Assessment of autistic disorder (autism) symptoms, primary and secondary, poses more challenging problems than ordinarily found in multisite randomized clinical trial (RCT) assessments. For example, subjects may be uncommunicative and extremely heterogeneous in problem presentation, and current pharmacological treatments are not likely to alter most core features of autism. The Autism Research Units on Pediatric Psychopharmacology (RUPP Autism Network) resolved some of these problems during the design of a risperidone RCT in children/adolescents. The inappropriateness of the usual anchors for a Clinical Global

Impression of Severity (CGI-S) was resolved by defining uncomplicated autism without secondary symptoms as a CGI-S of 3, mildly ill. The communication problems, compromising use of the patient as an informant, were addressed by several strategies, including careful questioning of care providers, rating scales, laboratory tests, and physical exams. The broad subject heterogeneity requires outcome measures sensitive to individual change over a wide spectrum of treatment response and side effects. The problems of neuropsychologically testing nonverbal, lower functioning, sometimes noncompliant subjects requires careful instrument selection/adaptation and flexible administration techniques. The problems of assessing low-end IQs, neglected by most standardized test developers, was resolved by an algorithm of test hierarchy. Scarcity of other autism-adapted cognitive and neuropsychological tests and lack of standardization required development of a new, specially adapted battery. Reliability on the Autism Diagnostic Interview (currently the most valid diagnostic instrument) and other clinician instruments required extensive cross-site training (in-person, videotape, and teleconference sessions). Definition of a treatment responder required focus on individually relevant target symptoms, synthesis of possible modest improvements in many domains, and acceptance of attainable though imperfect goals. The assessment strategy developed is implemented in a RCT of risperidone (McDougle et al., 2000) for which the design and other methodological challenges are described elsewhere (Scahill et al., 2000). Some of these problems and solutions are partially shared with RCTs of other treatments and other disorders.

6.113. Chez, M.G., Buchanan, C.P., Bagan, B.T., Hammer, M.S., McCarthy, K.S., Ovrutskaya, I., Nowinski, C.V., Cohen, Z.S. "Secretin and autism: a two-part clinical investigation." *J Autism Dev Disord* 2000 Apr;30(2):87-94. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Recent anecdotal reports have touted the gastrointestinal (GI) hormone secretin as a treatment modality for autism, though there is little clinical evidence or literature to support its viability. We undertook a two-part clinical trial to investigate these claims. Fifty-six patients (49 boys, 7 girls, mean age = 6.4 years, SD = 2.7) enrolled in an open-label trial of secretin, during which they received one injection of the hormone (2 IU/kg). All subjects were evaluated by their parents at baseline and follow-up visits (3-6 weeks later, M = 3.7, SD = 1.4 weeks) with Childhood Autism Rating Scales (CARS). Thirty-four patients were labeled with Pervasive Developmental Disorder Not Otherwise Specified, and 22 met diagnostic criteria for Autistic Disorder. Forty-five patients were concurrently on other drug treatments. At follow-up, some reported minimal but potentially significant improvements including changes in GI symptoms, expressive and/or receptive language function, and improved awareness and social interactions. No adverse effects were reported or observed. Subsequently, 17 of the most responsive patients from Study 1 began a double-blind trial that also included 8 newly enrolled patients. Patients in this second study were alternatively entered into

one of two groups and received injections of secretin or placebo with crossover at 4 weeks. Patients from Study 1 entered into Study 2 at an average of 6.5 (SD = 0.8) weeks after beginning Study 1. Results of both inquiries indicate that although treatment with secretin was reported to cause transient changes in speech and behavior in some children, overall it produced few clinically meaningful changes when compared to children given placebo injections.

6.114. Kraijer, D. "Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder." *J Autism Dev Disord* 2000 Feb;30(1):39-47. Publication Types: Review, Review, Tutorial.

Stichting Hendrik van Boeijen, Assen, The Netherlands.

A review is presented of the investigations carried out concerning the adaptive behavior of persons with the dual disability of mental retardation and autism/PDD. A close correspondence is found between the results obtained by means of a Dutch set of scales, the SRZ, SGZ, and SMZ, and those obtained by means of the Vineland Adaptive Behavior Scales. Compared with matched nonautistic persons, the performance of dually disabled persons is found to be particularly poor in the domain Social Skills/Socialization and somewhat less poor in the domain Communication. Performance of the two categories does not differ in the domains Self Help/Daily Living Skills and Gross Motor Skills/Motor Skills. As a net result, persons of the dually disabled category are found to obtain comparatively low total scores for social competency, the SRZ-Total/Adaptive Behavior Composite. In addition, autistic mentally retarded persons are found to display more maladaptive behavior. For comparative studies in the mental retardation field the use of level of Self Help/Daily Living Skills and, to a lesser extent, level of Gross Motor Skills/Motor Skills are recommended as suitable matching variables.

6.115. Novotny, S., Hollander, E., Allen, A., Mosovich, S., Aronowitz, B., Cartwright, C., DeCria, C., Dolgoff-Kaspar, R. "Increased growth hormone response to sumatriptan challenge in adult autistic disorders." *Psychiatry Res* 2000 May 15;94(2):173-7. Publication Types: Clinical Trial, Randomized Controlled Trial.

Seaver Autism Research Center, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029-6574, USA.

Serotonergic (5-HT) abnormalities have been documented in autism. To assess sensitivity of the 5-HT_{1d} receptor, growth hormone response to the 5-HT_{1d} receptor agonist sumatriptan was studied in adult autistic patients and matched normal controls. In this study, 11 adult patients with autism or Asperger's disorder were compared with nine matched controls. All subjects were randomized to single dose sumatriptan (6 mg SQ) and placebo challenges, separated by a 1-week interval, and growth hormone was measured before and during the challenges. The results showed a highly significant diagnosis x drug x time interaction on repeated measure analysis covaried for baseline. This suggests that

autistic patients had significantly greater growth hormone response to sumatriptan than normal controls, independent of placebo effects. Therefore, abnormalities in 5-HT regulation in autism may be related to increased sensitivity of the 5-HT_{1d} inhibitory receptor in autism.

6.116. Scheuffgen, K., Happe, F., Anderson, M., Frith, U. "High "intelligence," low "IQ"? Speed of processing and measured IQ in children with autism." *Dev Psychopathol* 2000 Winter;12(1):83-90.

Institute of Cognitive Neuroscience and Department of Psychology, University College London, UK.

The uneven profile of performance on standard assessments of intelligence and the high incidence of savant skills have prompted interest in the nature of intelligence in autism. The present paper reports the first group study of speed of processing in children with autism (IQ 1 SD below average) using an inspection time task. The children with autism showed inspection times as fast as an age-matched group of young normally developing children (IQ 1 SD above average). They were also significantly faster than mentally handicapped children without autism of the same age, even when these groups were pairwise matched on Wechsler IQ. To the extent that IT tasks tap individual differences in basic processing efficiency, children with autism in this study appear to have preserved information processing capacity despite poor measured IQ. These findings have implications for the role of general and specific cognitive systems in knowledge and skill acquisition: far from showing that children with autism are unimpaired, we suggest that our data may demonstrate the vital role of social insight in the development of manifest "intelligence."

6.117. Schultz, R.T., Gauthier, I., Klin, A., Fulbright, R.K., Anderson, A.W., Volkmar, F., Skudlarski, P., Lacadie, C., Cohen, D.J., Gore, J.C. "Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome." *Arch Gen Psychiatry* 2000 Apr;57(4):331-40.

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BACKGROUND: Recognition of individual faces is an integral part of both interpersonal interactions and successful functioning within a social group. Therefore, it is of considerable interest that individuals with autism and related conditions have selective deficits in face recognition (sparing nonface object recognition). **METHOD:** We used functional magnetic resonance imaging (fMRI) to study face and subordinate-level object perception in 14 high-functioning individuals with autism or Asperger syndrome (the autism group), in comparison with 2 groups of matched normal controls (normal control group 1 [NC1] and normal control group 2 [NC2]) (n = 14 for each). Regions of interest (ROIs) were defined in NC1 and then applied in comparisons between NC2 and the autism group. Regions of interest were also defined in NC2 and then applied to comparisons between NC1 and the autism group as a replication study. **RESULTS:**

In the first set of comparisons, we found significant task x group interactions for the size of activation in the right fusiform gyrus (FG) and right inferior temporal gyri (ITG). Post hoc analyses showed that during face (but not object) discrimination, the autism group had significantly greater activation than controls in the right ITG and less activation of the right FG. The replication study showed again that the autism group used the ITG significantly more for processing faces than the control groups, but for these analyses, the effect was now on the left side. Greater ITG activation was the pattern found in both control groups during object processing. CONCLUSIONS: Individuals with autism spectrum disorders demonstrate a pattern of brain activity during face discrimination that is consistent with feature-based strategies that are more typical of nonface object perception.

6.118. Miles, J.H., Hillman, R.E. "Value of a clinical morphology examination in autism." *Am J Med Genet* 2000 Apr 10;91(4):245-53.

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In an effort to delineate more homogeneous autism subgroups for genetic study, we evaluated 133 consecutive individuals referred to the University of Missouri Autism Center. Each index case underwent a diagnostic evaluation, including a clinical morphology examination, laboratory studies, brain MRI, EEG, and collection of historical, medical, and family data. The 71% (94/133) who fulfilled DSM-IV and CARS autism diagnostic criteria were included in this study. Six of 94 were diagnosed with a known genetic disorder. Of the remaining 88 with apparently "idiopathic autism," 58% (51/88) were phenotypically normal, 22% (19/88) were clearly abnormal, and for 20% (18/88) the clinical morphology examination was equivocal. The percentage of phenotypically abnormal individuals is higher than generally thought and disagrees with the perception that children with autism are usually normally formed. The phenotypically abnormal individuals were 10 times more likely to be diagnosed with a known genetic syndrome (21% vs. 2%) and were more than twice as likely (29% vs. 14%) to have structurally abnormal brain MRIs than the phenotypically normal propositi. Moreover, the male to female ratio correlated with the presence of physical anomalies. The total study group had a male to female ratio of 4.2:1; the morphologically normal subgroup, defined on the basis of a normal physical examination, had a sex ratio of 7.5:1 and the normal subgroup, defined on the basis of both a normal physical examination and a structurally normal brain by MRI had a 23:1 sex ratio. For the phenotypically abnormal subgroup, the sex ratio was 1.7:1. Since differences in sex ratio are presumably a reflection of differences in genetic constitution, we postulate that the phenotypically normal subgroup of individuals with "idiopathic autism" is genetically different from the phenotypically abnormal individuals and that differences in the sex ratio in different autism populations is one indicator of a population's genetic heterogeneity. Copyright 2000 Wiley-Liss, Inc.

6.119. Gottschalk, J.M., Libby, M.E., Graff, R.B. "The effects of establishing operations on preference assessment outcomes." *J Appl Behav Anal* 2000 Spring;33(1):85-8.

Northeastern University, USA.

Preference assessments were conducted for 4 individuals with developmental disabilities across conditions of (a) control, allowing equal access to all stimuli prior to the preference assessment; (b) deprivation, allowing no access to one stimulus for 48 hr prior to the assessment; and (c) satiation, allowing free access to one stimulus for 10 min immediately prior to the assessment. Deprivation resulted in increased preference, whereas satiation resulted in decreased preference compared to control conditions.

6.120. Giovanardi Rossi, P., Posar, A., Parmeggiani, A. "Epilepsy in adolescents and young adults with autistic disorder." *Brain Dev* 2000 Mar;22(2):102-6.

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Since the first description by Kanner (1943) the association between autistic disorder (AD) and epilepsy has been observed in 4-42% of patients. Some authors reported that seizures prevailed in adolescence but a systematic investigation has never been undertaken. We examined retrospectively 60 patients divided into two groups (with and without epilepsy and EEG paroxysmal abnormalities) with AD unrelated to a congenital or acquired encephalopathy (mean age 17 years 2 months). The aim was to investigate epilepsy, EEG paroxysmal abnormalities and possible etiological factors. The prevalence of epilepsy was 38.3%, much higher than that in a normal population of a similar age (6.6 per thousand). The prevalence of EEG paroxysmal abnormalities without epilepsy was 6.7%, higher than that in a population of adolescents and adults with psychiatric pathologies (2.6%). Seizure onset was after age 12 years in 66.7% of cases. The most common type of epilepsy was partial in 65.2% and four patients (17.4%) had a benign childhood epilepsy with centro-temporal spikes. At the last observation 44.4% of patients had been seizure-free for 2 years or more. There were no organic factors influencing the development of epilepsy but familial and personal antecedents, mental retardation and CT scan/MRI data may suggest an early brain dysfunction responsible for AD and epilepsy.

6.121. Hendry, C.N. "Childhood disintegrative disorder: should it be considered a distinct diagnosis?" *Clin Psychol Rev* 2000 Jan;20(1):77-90. Publication Types: Review, Review, Tutorial.

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First termed Dementia Infantilis by Theodore Heller in 1908, Childhood Disintegrative Disorder (CDD) has had a history longer than that of Autistic Disorder. Presently, CDD is classified as a Pervasive Developmental Disorder in the fourth edition of the Diagnostic and Statistical Manual of Mental

Disorders. The characteristics most often cited as distinguishing CDD from Autistic Disorder, another one of the Pervasive Developmental Disorders, is the age of onset and evidence of normal development prior to the presence of symptomatology. Otherwise, the behavioral symptoms of CDD and Autistic Disorder are strikingly similar. The purpose of this article is to provide a historical background on CDD, examine the evolution of diagnostic criteria, review the existing literature pertaining to the disorder, and, finally, to draw conclusions regarding the validity of CDD as a distinct diagnosis with reference to current and alternative classification approaches.

6.122. Berument, S.K., Rutter, M., Lord, C., Pickles, A., Bailey, A. "Autism screening questionnaire: diagnostic validity." *Br J Psychiatry* 1999 Nov;175:444-51.

MRC Child Psychiatry Unit, Institute of Psychiatry, London.

BACKGROUND: Good interview and diagnostic measures for autism and other pervasive developmental disorders (PDDs) are available but there is a lack of a good screening questionnaire. **AIMS:** To develop and test a screening questionnaire based on items in the best available diagnostic interview—the Autism Diagnostic Interview—Revised (ADI-R). **METHOD:** A 40-item scale, the Autism Screening Questionnaire (ASQ), was developed and tested on a sample of 160 individuals with PDD and 40 with non-PDD diagnoses. **RESULTS:** The ASQ has good discriminative validity with respect to the separation of PDD from non-PDD diagnoses at all IQ levels, with a cut-off of 15 proving most effective. The differentiation between autism and other varieties of PDD was weaker. **CONCLUSIONS:** The ASQ is an effective screening questionnaire for PDD.

6.123. Malhotra, S., Gupta, N. "Childhood disintegrative disorder." *J Autism Dev Disord* 1999 Dec;29(6):491-8. Publication Types: Review, Review, Tutorial.

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Childhood disintegrative disorder (CDD) is a clinical syndrome characterized by disintegration of mental functions and regression of acquired language and intellectual functions after a period of normal development typically of 3 to 4 years. Although recognized for many years, research on this condition is less advanced than that in autism. Epidemiological data are limited but the condition is much less common than autism. The relationship of this condition to autism remains the topic of debate. Neuropathological and other medical conditions are sometimes associated with the disorder but contrary to earlier belief this is not typical. Collaborative research would facilitate our understanding of this condition.

6.124. Waller, S.A., Armstrong, K.J., McGrath, A.M., Sullivan, C.L. "A review of the diagnostic methods reported in the *Journal of Autism and Developmental Disorders*." *J Autism Dev Disord* 1999 Dec;29(6):485-90. Publication Types: Review, Review, Tutorial.

Western Michigan University, Kalamazoo 49008, USA.

This review summarizes subject selection and diagnostic procedures documented in the *Journal of Autism and Developmental Disorders*. One hundred forty-two empirical articles published between February 1993 and April 1997 were examined. Reviewers independently evaluated articles using a coding instrument developed by the authors. Results indicated that a majority of researchers reported the use of one or more standard diagnostic criteria in classifying their subjects. However, numerous studies did not report the methods by which the diagnostic criteria were quantified or applied. Additionally, there was a lack of clear specification of inclusion and exclusion criteria for comorbid disorders. Improving the documentation of diagnostic practices in research on autism will benefit researchers and practitioners.

6.125. Filipek, P.A., Accardo, P.J., Baranek, G.T., Cook, E.H. Jr., Dawson, G., Gordon, B., Gravel, J.S., Johnson, C.P., Kallen, R.J., Levy, S.E., Minshew, N.J., Ozonoff, S., Prizant, B.M., Rapin, I., Rogers, S.J., Stone, W.L., Teplin, S., Tuchman, R.F., Volkmar, F.R. "The screening and diagnosis of autistic spectrum disorders." *J Autism Dev Disord* 1999 Dec;29(6):439-84. Publication Types: Review, Review, Tutorial.

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The Child Neurology Society and American Academy of Neurology recently proposed to formulate Practice Parameters for the Diagnosis and Evaluation of Autism for their memberships. This endeavor was expanded to include representatives from nine professional organizations and four parent organizations, with liaisons from the National Institutes of Health. This document was written by this multidisciplinary Consensus Panel after systematic analysis of over 2,500 relevant scientific articles in the literature. The Panel concluded that appropriate diagnosis of autism requires a dual-level approach: (a) routine developmental surveillance, and (b) diagnosis and evaluation of autism. Specific detailed recommendations for each level have been established in this document, which are intended to improve the rate of early suspicion and diagnosis of, and therefore early intervention for, autism.

6.126. Bristol-Power, M.M., Spinella, G. "Research on screening and diagnosis in autism: a work in progress." *J Autism Dev Disord* 1999 Dec;29(6):435-8. Publication Types: Review, Review, Tutorial.

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In June 1998, the National Institutes of Health Autism Coordinating Committee (NIH/ACC) invited representatives of 13 major medical and other professional academies and associations and six national autism parent research organizations to review research data on screening and diagnosis of autism spectrum disorders. Ten review papers and more than 4,000 publications were consulted in this effort. This paper highlights some promising areas for research identified in this process. One of the highest priorities is the search for the ultimate diagnostic indicator, a biological

marker(s), for example, genetic, metabolic, immunologic, neurologic, that will distinguish autism unequivocally from other developmental disabilities. In the interim, research on infant screening and diagnosis might lower the threshold age for diagnosis to 8-12 months. The role of sensory-motor disorders in early diagnosis needs further research. Earlier and better diagnosis of co-occurring, potentially treatable disorders, including epileptic and epileptiform disorders, has implications both for diagnosis and treatment. Pharmacogenetic and pharmacogenomic research strategies could help diagnose subtypes and responders versus nonresponders to potential treatments. Better endpoints and outcome measures are needed, including improved procedures for cognitive and neuropsychological testing, more knowledge about verbal and nonverbal communication milestones, and less invasive and more sensitive neuroimaging measures. Critical questions remain regarding regression after apparently normal development, and about possible environmental precipitants. Finally, field trials of the reliability and validity of screening and diagnosis using the newly developed practice guidelines are needed.

6.127. Howlin, P., Asgharian, A. "The diagnosis of autism and Asperger syndrome: findings from a survey of 770 families." *Dev Med Child Neurol* 1999 Dec;41(12):834-9.

Department of Psychology, St George's Hospital Medical School, London, UK.

As part of a wider survey of parents of children with autistic spectrum disorders in the UK, the diagnostic experiences of 614 parents of children with autism and 156 with Asperger syndrome were compared. Although the ages of the children in the two groups were very similar at the time of the survey, parents of children given a diagnosis of Asperger syndrome had experienced significantly longer delays and greater frustration in obtaining a diagnosis than those with a child with autism. In the 'autism group' the average age when diagnosis was confirmed was around 5.5 years; in the 'Asperger group' it was 11 years. Parents of children with a diagnosis of autism were generally aware of problems in their child's development by 18 months of age; in the Asperger group concerns emerged later, at around 30 months of age. Initial worries in both groups centred around abnormal social development but parents of children with Asperger syndrome were less likely to have noted communication problems. Stereotyped or repetitive behaviours were not prominent in the early years in either group. Despite the problems inherent in data collected by postal survey, many of the findings of this study are supported by other research. The practical implications of delayed diagnosis, especially in the case of more able children with Asperger syndrome are discussed.

6.128 Volkmar, F., Cook, E. Jr., Pomeroy, J., Realmuto, G., Tanguay, P. "Summary of the Practice Parameters for the Assessment and Treatment of Children, Adolescents, and Adults with Autism and other Pervasive Developmental Disorders. American Academy of Child and Adolescent Psychiatry." *J Am Acad Child Adolesc Psychiatry* 1999 Dec;38(12):1611-6. Publication Types: Guideline, Practice Guideline.

This summary provides an overview of the assessment and treatment recommendations contained in the Practice Parameters for the Assessment and Treatment of Children, Adolescents, and Adults With Autism and Other Pervasive Developmental Disorders. The parameters were written to aid clinicians in the assessment and treatment of children and adolescents with autism and other pervasive developmental disorders. Autism and the related pervasive developmental disorders are characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills, which arise in the first years of life. Although frequently associated with mental retardation, these conditions are distinctive in terms of their course and treatment. These conditions have a wide range of syndrome expression, and their management presents particular challenges for clinicians. Individuals with these conditions can present for clinical care at any point in development. The multiple developmental and behavioral problems associated with these conditions often require the care of multiple providers; coordination of services and advocacy for individuals and their families is important. Early, sustained intervention is indicated, as is the use of various treatment modalities (e.g., pharmacotherapy, special education, speech/communication therapy, and behavior modification).

6.129. Aylward, E.H., Minshew, N.J., Goldstein, G., Honeycutt, N.A., Augustine, A.M., Yates, K.O., Barta, P.E., Pearlson, G.D. "MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults." *Neurology* 1999 Dec 10;53(9):2145-50.

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OBJECTIVE: To determine whether volumes of hippocampus and amygdala are abnormal in people with autism. **BACKGROUND:** Neuropathologic studies of the limbic system in autism have found decreased neuronal size, increased neuronal packing density, and decreased complexity of dendritic arbors in hippocampus, amygdala, and other limbic structures. These findings are suggestive of a developmental curtailment in the maturation of the neurons and neuropil. **METHODS:** Measurement of hippocampus, amygdala, and total brain volumes from 1.5-mm coronal, spoiled gradient-recalled echo MRI scans in 14 non-mentally retarded autistic male adolescents and young adults and 14 individually matched, healthy community volunteers. **RESULTS:** Amygdala volume was significantly smaller in the autistic subjects, both with ($p = 0.006$) and without ($p = 0.01$) correcting for total brain volume. Total brain volume and absolute hippocampal volume did not differ significantly between groups, but hippocampal volume, when corrected for total brain volume, was significantly reduced ($p = 0.04$) in the autistic subjects. **CONCLUSIONS:** There is a reduction in the volume of amygdala and hippocampus in people with autism, particularly in relation to total brain volume. The histopathology of autism suggests that these volume reductions are related to a reduction in dendritic tree and neuropil development, and likely reflect the underdevelopment of the neural connections of limbic

structures with other parts of the brain, particularly cerebral cortex.

6.130. Kobayashi, R. "Physiognomic perception, vitality affect and delusional perception in autism." *Psychiatry Clin Neurosci* 1999 Oct;53(5):549-55. Publication Types: Review, Review, Tutorial.

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The relationship between autism and schizophrenia has been denied from the symptomatological and epidemiological standpoints. However, the mechanism whereby psychotic symptoms appear in association with autism has not been investigated at any length. Therefore, an investigation was conducted on how the unique modes of perception in autism are related to the psychotic symptoms observed. Through the therapy of one case of adolescent autism, the author points out the existence of physiognomic perception and vitality affect as characteristic modes of perception in autism. It was inferred that should autistics be placed under circumstances forcing them to withdraw from open communalism, their unique interpretation of the environmental world could give rise to psychopathological phenomena which would be considered delusional perception.

6.131. Freeman, B.J., Del'Homme, M., Guthrie, D., Zhang, F. "Vineland Adaptive Behavior Scale scores as a function of age and initial IQ in 210 autistic children." *J Autism Dev Disord* 1999 Oct;29(5):379-84.

Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine/NPI 90024, USA.

Human growth modeling statistics were utilized to examine how Vineland Adaptive Behavior Scale (VABS) scores changed in individuals with autistic disorder as a function of both age and initial IQ. Results revealed that subjects improved with age in all domains. The rate of growth in Communication and Daily Living Skills was related to initial IQ while rate of growth in Social Skills was not. Results should provide hope for parents and further support for the importance of functional social-communication skills in the treatment of autism.

6.132. Baron-Cohen, S., Schill, V.L., Izaguirre, J., Hornsey, H., Robertson, M.M. "The prevalence of Gilles de la Tourette syndrome in children and adolescents with autism: a large scale study." *Psychol Med* 1999 Sep;29(5):1151-9.

Department of Experimental Psychology and Psychiatry, University of Cambridge.

BACKGROUND: An earlier small-scale study of children with autism revealed that 8.1% of such patients were co-morbid for Gilles de la Tourette syndrome (GTS). The present study is a large scale test of whether this result replicates. **METHOD:** Four hundred and forty-seven pupils from nine schools for children and adolescents with autism were screened for the presence of motor and vocal tics. **RESULTS:** Subsequent family interviews confirmed the co-morbid diagnosis of definite GTS

in 19 children, giving a prevalence rate of 4.3%. A further 10 children were diagnosed with probable GTS (2.2%). **CONCLUSIONS:** These results indicate that the rate of GTS in autism exceeds that expected by chance, and the combined rate (6.5%) is similar to the rates found in the smaller-scale study. Methodological considerations and alternative explanations for an increased prevalence are discussed.

6.133. Manes, F., Piven, J., Vrancic, D., Nanclares, V., Plebst, C., Starkstein, S.E. "An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals." *J Neuropsychiatry Clin Neurosci* 1999 Fall;11(4):470-4.

Department of Neuropsychiatry, Raul Carrea Institute of Neurological Research-FLENI, Buenos Aires, Argentina.

The areas of seven subregions of the corpus callosum and three subregions of the cerebellum were examined on midsagittal magnetic resonance imaging scans of 27 low-IQ autistic individuals and 17 nonautistic individuals of comparable mental age. Autistic individuals had a significantly smaller corpus callosum (most marked in the body). No significant between-group differences were found in cerebellum areas. Results demonstrate that abnormalities of the corpus callosum reported in high-functioning autistic individuals are also present in autistic individuals with mental retardation and extend previous reports showing no evidence for a selective hypoplasia of cerebellar lobules VI-VII.

6.134. Goldberg, J., Szatmari, P., Nahmias, C. "Imaging of autism: lessons from the past to guide studies in the future." *Can J Psychiatry* 1999 Oct;44(8):793-801.

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OBJECTIVE: To review the scientific literature on the imaging of autism with a view to understanding how imaging can contribute to future studies. **METHODS:** Medline was searched, and bibliographies from retrieved articles were reviewed. Inclusion criteria were a diagnosis of autism according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, third edition or later, and a control group without autism. **RESULTS:** The field suffers from a lack of replication studies and poor methodology in terms of not controlling for confounding variables. Enlarged brain size, particularly in the temporoparietal brain region, and decreased size of the posterior corpus callosum are the only findings that have been independently replicated. **CONCLUSION:** Future imaging studies should attempt to investigate more homogeneous subgroups of patients such as those with "the lesser variant of PDD" and high-functioning patients with PDD who do not have comorbid medical conditions. A different approach, examining the individual behaviours that constitute the PDD spectrum and exploring these separately along with other associated variables such as neuropsychological deficits, structural and functional brain abnormalities, and genetic information could help identify biological mechanisms that do not follow diagnostic boundaries.

6.135. Abell, F., Krams, M., Ashburner, J., Passingham, R., Friston, K., Frackowiak, R., Happe, F., Frith, C., Frith, U. "The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans." *Neuroreport* 1999 Jun 3;10(8):1647-51.

Institute of Cognitive Neuroscience and Department of Psychology, London, UK.

Autism is a biological disorder which affects social cognition, and understanding brain abnormalities of the former will elucidate the brain basis of the latter. We report structural MRI data on 15 high-functioning individuals with autistic disorder. A voxel-based whole brain analysis identified grey matter differences in an amygdala centered system relative to 15 age- and IQ-matched controls. Decreases of grey matter were found in anterior parts of this system (right paracingulate sulcus, left inferior frontal gyrus). Increases were found in posterior parts (amygdala/peri-amygdaloid cortex, middle temporal gyrus, inferior temporal gyrus), and in regions of the cerebellum. These structures are implicated in social cognition by animal, imaging and histopathological studies. This study therefore provides converging evidence of the physiological basis of social cognition.

6.136. Kemner, C., van der Gaag, R.J., Verbaten, M., van Engeland, H. "ERP differences among subtypes of pervasive developmental disorders." *Biol Psychiatry* 1999 Sep 15;46(6):781-9.

Utrecht University, Department of Child and Adolescent Psychiatry, The Netherlands.

BACKGROUND: Children with multiple complex developmental disorder (MCDD) have been distinguished from autistic children on the basis of chart reviews. It was questioned whether it is possible to find other, e.g., event-related potential (ERP), evidence for this assertion. **METHODS:** ERPs were measured in response to stimuli in a visual oddball task in autistic, MCDD, attention deficit disorder, dyslexic, and normal control children, to study whether ERP peaks can be used to distinguish autistic and MCDD children, and to classify the aforementioned groups. **RESULTS:** It was found that the P3 at four different leads and the frontal Nc showed differences among the groups, and that the autistic and MCDD groups differed from each other as well as from the other groups. Also, it was found that, using discriminant analyses in which these parameters were included, children were classified above chance level. Especially in the MCDD group, a high percentage of correct classification was seen. **CONCLUSIONS:** ERP parameters indicate that autistic and MCDD children might differ in underlying pathology and might therefore, better be regarded as two separate diagnostic entities.

6.137. Berney, T.P., Ireland, M., Burn, J. "Behavioural phenotype of Cornelia de Lange syndrome." *Arch Dis Child* 1999 Oct;81(4):333-6.

Fleming Nuffield Child Psychiatry Unit, Burden Terrace, Newcastle upon Tyne NE2 3AE, UK.

A postal questionnaire was used to study 49 individuals with Cornelia de Lange syndrome (including both the classical and the mild forms) to ascertain behavioural phenotype. Ages ranged from early childhood to adulthood (mean age, 10.2 years; SD, 7.8) and the degree of mental retardation from borderline (10%), through mild (8%), moderate (18%), and severe (20%) to profound (43%). A wide variety of symptoms occurred frequently, notably hyperactivity (40%), self injury (44%), daily aggression (49%), and sleep disturbance (55%). These correlated closely with the presence of an autistic like syndrome and with the degree of mental retardation. The frequency and severity of disturbance, continuing beyond childhood, is important when planning the amount and duration of support required by parents.

6.138. Lewine, J.D., Andrews, R., Chez, M., Patil, A.A., Devinsky, O., Smith, M., Kanner, A., Davis, J.T., Funke, M., Jones, G., Chong, B., Provencal, S., Weisend, M., Lee, R.R., Orrison, W.W. Jr. "Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders." *Pediatrics* 1999 Sep;104(3 Pt 1):405-18.

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BACKGROUND: One-third of children diagnosed with autism spectrum disorders (ASDs) are reported to have had normal early development followed by an autistic regression between the ages of 2 and 3 years. This clinical profile partly parallels that seen in Landau-Kleffner syndrome (LKS), an acquired language disorder (aphasia) believed to be caused by epileptiform activity. Given the additional observation that one-third of autistic children experience one or more seizures by adolescence, epileptiform activity may play a causal role in some cases of autism. **OBJECTIVE:** To compare and contrast patterns of epileptiform activity in children with autistic regressions versus classic LKS to determine if there is neurobiological overlap between these conditions. It was hypothesized that many children with regressive ASDs would show epileptiform activity in a multifocal pattern that includes the same brain regions implicated in LKS. **DESIGN:** Magnetoencephalography (MEG), a noninvasive method for identifying zones of abnormal brain electrophysiology, was used to evaluate patterns of epileptiform activity during stage III sleep in 6 children with classic LKS and 50 children with regressive ASDs with onset between 20 and 36 months of age (16 with autism and 34 with pervasive developmental disorder-not otherwise specified). Whereas 5 of the 6 children with LKS had been previously diagnosed with complex-partial seizures, a clinical seizure disorder had been diagnosed for only 15 of the 50 ASD children. However, all the children in this study had been reported to occasionally demonstrate unusual behaviors (eg, rapid blinking, holding of the hands to the ears, unprovoked crying episodes, and/or brief staring spells) which, if exhibited by a normal child, might be interpreted as indicative of a subclinical epileptiform condition. MEG data were compared with simultaneously recorded electroencephalography (EEG) data, and with data from previous 1-hour and/or 24-hour clinical EEG, when available. Multiple-dipole, spatiotemporal modeling was used

to identify sites of origin and propagation for epileptiform transients. **RESULTS:** The MEG of all children with LKS showed primary or secondary epileptiform involvement of the left intra/perisylvian region, with all but 1 child showing additional involvement of the right sylvian region. In all cases of LKS, independent epileptiform activity beyond the sylvian region was absent, although propagation of activity to frontal or parietal regions was seen occasionally. MEG identified epileptiform activity in 41 of the 50 (82%) children with ASDs. In contrast, simultaneous EEG revealed epileptiform activity in only 68%. When epileptiform activity was present in the ASDs, the same intra/perisylvian regions seen to be epileptiform in LKS were active in 85% of the cases. Whereas primary activity outside of the sylvian regions was not seen for any of the children with LKS, 75% of the ASD children with epileptiform activity demonstrated additional nonsylvian zones of independent epileptiform activity. Despite the multifocal nature of the epileptiform activity in the ASDs, neurosurgical intervention aimed at control has led to a reduction of autistic features and improvement in language skills in 12 of 18 cases. **CONCLUSIONS:** This study demonstrates that there is a subset of children with ASDs who demonstrate clinically relevant epileptiform activity during slow-wave sleep, and that this activity may be present even in the absence of a clinical seizure disorder. MEG showed significantly greater sensitivity to this epileptiform activity than simultaneous EEG, 1-hour clinical EEG, and 24-hour clinical EEG. The multifocal epileptiform pattern identified by MEG in the ASDs typically includes the same perisylvian brain regions identified as abnormal in LKS. When epileptiform activity is present in the ASDs, therapeutic strategies (antiepileptic drugs, steroids, and even neurosurgery) aimed at its control can lead to a significant

6.139. Zanolli, K., Daggett, J., Ortiz, K., Mullins, J. "Using rapidly alternating multiple schedules to assess and treat aberrant behavior in natural settings." *Behav Modif* 1999 Jul;23(3):358-78.

University of Kansas, USA.

The validity of using rapidly alternating multiple schedules (RAMS) as a method for assessing and treating aggression and disruptive behavior was demonstrated by using the naturally occurring reinforcers identified in the RAMS to develop treatments that were experimentally tested. The RAMS consists of a series of 2-minute components in which a naturally occurring consequence is applied contingent on the target's behavior, alternated with components in which the consequence is not applied, with no break between components. The aggressive and disruptive behaviors of four 2- to 11-year-old children were analyzed and treated in school and home settings. The RAMS analyses yielded clear results about the reinforcing function of naturally occurring consequences in all cases, and the treatments using the reinforcers identified in the RAMS were all effective. The possible uses of the RAMS as an efficient, ecologically and experimentally valid tool for clinical assessment are discussed.

6.140. Nass, R., Devinsky, O. "Autistic regression with rolandic spikes." *Neuropsychiatry Neuropsychol Behav Neurol* 1999 Jul;12(3):193-7.

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OBJECTIVE: This study was designed to further define the electroencephalographic abnormalities seen in the Landau-Kleffner syndrome variants and the associated clinical features. **BACKGROUND:** Landau-Kleffner syndrome is rare, but its putative variants are more common. **METHOD:** We report two patients with centro-temporal spikes, autistic epileptiform regression, and variably prominent oro-motor symptoms. **RESULTS:** The epileptic aphasia pattern found among patients with prominent Rolandic spikes may more frequently involve expressive language than is seen in the typical Landau-Kleffner syndrome, where verbal auditory agnosia is the rule. **CONCLUSIONS:** This clinical difference likely reflects the location of the epileptiform activity (centrotemporal as opposed to anterior or mid-temporal) on buccal-lingual function, vocalization, and language production.

6.141. Cox, A., Klein, K., Charman, T., Baird, G., Baron-Cohen, S., Swettenham, J., Drew, A., Wheelwright, S. "Autism spectrum disorders at 20 and 42 months of age: stability of clinical and ADI-R diagnosis." *J Child Psychol Psychiatry* 1999 Jul;40(5):719-32.

Bloomfield Clinic and Newcomen Centre, Guy's King's College, and St Thomas' Medical School, London, UK.

The association between, and stability of, clinical diagnosis and diagnosis derived from the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) was examined in a sample of prospectively identified children with childhood autism and other pervasive developmental disorders assessed at the age of 20 months and 42 months. Clinical diagnosis of autism was stable, with all children diagnosed with childhood autism at age 20 months receiving a diagnosis of childhood autism or a related pervasive developmental disorder (PDD) at age 42 months. Clinical diagnosis of childhood autism was also reasonably sensitive, with all children who went on to receive a clinical diagnosis of childhood autism at 42 months being identified as having autism or PDD at 20 months. However, clinical diagnosis for PDD and Asperger's syndrome lacked sensitivity at 20 months, with several children who subsequently received these diagnoses at 42 months receiving diagnoses of language disorder or general developmental delay, as well as in two cases being considered clinically normal, at the earlier timepoint. The ADI-R was found to have good specificity but poor sensitivity at detecting childhood autism at 20 months; however, the stability of diagnosis from 20 to 42 months was good. In addition, the ADI-R at age 20 months was not sensitive to the detection of related PDDs or Asperger's syndrome. The continuity and discontinuity between behavioural abnormalities identified at both timepoints in the three domains of impairment in autism was examined, both in children who met final clinical criteria for an autistic

spectrum disorder, and for children with language disorder who did not, as well as for a small sample of typically developing children.

6.142. Vig, S., Jedrysek, E. "Autistic features in young children with significant cognitive impairment: autism or mental retardation?" *J Autism Dev Disord* 1999 Jun;29(3):235-48. Publication Types: Review, Review, Tutorial.

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This review addresses the issues and challenges related to the differential diagnosis of autism in preschool children with significant cognitive impairment. Issues affecting differential diagnosis include the use of traditional diagnostic guidelines for preschoolers with developmental delays, developmental changes in behavioral characteristics, the involvement of cognitive factors in symptom expression, and the overlap between autism and mental retardation in individuals with significant cognitive impairment. The usefulness of autistic features for differential diagnosis is explored in terms of the core deficits of autism.

6.143. Baranek, G.T. "Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age." *J Autism Dev Disord* 1999 Jun;29(3):213-24.

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This retrospective video study explored the usefulness of sensory-motor measures in addition to social behaviors as early predictors of autism during infancy. Three groups included 11 children with autism, 10 with developmental disabilities, and 11 typically developing children. Home videos were edited to obtain a 10-minute cross-section of situations at 9-12 months for each subject. Using interval scoring, raters coded several behavioral categories (i.e., Looking, Affect, Response to Name, Anticipatory Postures, Motor/Object Stereotypies, Social Touch, Sensory Modulation). Nine items, in combination, were found to discriminate the three groups with a correct classification rate of 93.75%. These findings indicate that subtle symptoms of autism are present at 9-12 months, and suggest that early assessment procedures need to consider sensory processing/sensory-motor functions in addition to social responses during infancy. Furthermore, prior to a time that they reported autistic symptoms, caregivers used compensatory strategies to increase the saliency of stimuli in order to engage their children more successfully; these strategies may provide a window for earlier diagnosis.

6.144. Murphy, G., Hall, S., Oliver, C., Kissi-Debra, R. "Identification of early self-injurious behaviour in young children with intellectual disability." *J Intellect Disabil Res* 1999 Jun;43 (Pt 3):149-63.

University of Kent, Canterbury, UK.

Very little is known about the early stages of self-injurious behaviour (SIB) in young children with developmental disabilities, even though there has been a great deal of research into the prevalence, assessment and treatment of well-established SIB in older individuals. In the present initial study, teachers in special schools for children under 11 years of age with severe intellectual disability and/or autism were asked to identify children who were beginning to show early self-injury (the index group). These children were then matched to classroom controls (of the same ability level and mobility), and teachers were interviewed about the children's behaviours and skills. The index children showed significantly more potential SIB than the control group children, but there was overlap between the groups in terms of percentage duration of potential SIB, suggesting that teachers do not find it easy to identify children with 'early' SIB. The index children's skills and problem behaviours, their sensory impairments and degree of autism did not differ significantly from those of the control group. When all the children showing any potential SIB were pooled together, it transpired that developmental age and degree of mobility were significantly correlated with percentage duration of SIB, suggesting that these characteristics may be important risk markers. The index children were also observed at 3-month intervals at school over the following 18 months and self-injury clearly escalated for some of the index children, while it did not do so for others. Using regression analysis, increases in SIB were shown to be associated only with the degree of concern expressed about the child's behaviour at time 1 by the teacher, no other variables predicting increases in SIB.

6.145. Sears, L.L., Vest, C., Mohamed, S., Bailey, J., Ranson, B.J., Piven, J. "An MRI study of the basal ganglia in autism." *Prog Neuropsychopharmacol Biol Psychiatry* 1999 May;23(4):613-24.

Mental Health Clinical Research Center, University of Iowa College of Medicine, USA.

1. High-resolution MRI scans were obtained from 35 relatively high-functioning persons with autism and 36 healthy controls, comparable in age, gender, and IQ. 2. Volumetric measurements were obtained from manual tracing of the bilateral caudate, putamen, and globus pallidus. 3. An increased volume of the caudate nuclei was found in subjects with autism. Caudate enlargement was proportional to increased total brain volume in subjects with autism. 4. Caudate volume was associated with compulsions and rituals, difficulties with minor change, and complex motor mannerisms in autism. 5. Based on evidence of caudate abnormalities, a second MRI study was completed which replicated the finding of caudate enlargement in autism using an independent sample. 6. The caudate may be part of an abnormal distributed neural network in autism and involved in the ritualistic—repetitive behaviors of the disorder.

6.146. Ring, H.A., Baron-Cohen, S., Wheelwright, S., Williams, S.C., Brammer, M., Andrew, C., Bullmore, E.T. "Cerebral correlates of preserved cognitive skills in autism: a functional MRI study of embedded figures task performance." *Brain* 1999 Jul;122 (Pt 7):1305-15.

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When considering the cognitive abilities of people with autism, the majority of studies have explored domains in which there are deficits. However, on tests of local processing and visual search, exemplified by the Embedded Figures Task (EFT), people with autism have been reported to demonstrate superiority over normal controls. This study employed functional MRI of subjects during the performance of the EFT to test the hypothesis that normal subjects and a group with autism would activate different brain regions and that differences in the patterns of these regional activations would support distinct models of cerebral processing underlying EFT performance in the two groups. It was found that several cerebral regions were similarly activated in the two groups. However, normal controls, as well as demonstrating generally more extensive task-related activations, additionally activated prefrontal cortical areas that were not recruited in the group with autism. Conversely, subjects with autism demonstrated greater activation of ventral occipitotemporal regions. These differences in functional anatomy suggest that the cognitive strategies adopted by the two groups are different: the normal strategy invokes a greater contribution from working memory systems while the autistic group strategy depends to an abnormally large extent on visual systems for object feature analysis. This interpretation is discussed in relation to a model of autism which proposes a predisposition towards local rather than global modes of information processing.

6.147. Ehlers, S., Gillberg, C., Wing, L. "A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children." *J Autism Dev Disord* 1999 Apr;29(2):129-41. Publication Types: Clinical Trial.

Department of Child and Adolescent Psychiatry, Goteborg University, Sahlgren University Hospital, Annedals Clinics, Sweden.

The high-functioning Autism Spectrum Screening Questionnaire (ASSQ) is a 27-item checklist for completion by lay informants when assessing symptoms characteristic of Asperger syndrome and other high-functioning autism spectrum disorders in children and adolescents with normal intelligence or mild mental retardation. Data for parent and teacher ratings in a clinical sample are presented along with various measures of reliability and validity. Optimal cutoff scores were estimated, using Receiver Operating Characteristic analysis. Findings indicate that the ASSQ is a useful brief screening device for the identification of autism spectrum disorders in clinical settings.

6.148. Rapin, I. "Appropriate investigations for clinical care versus research in children with autism." *Brain Dev* 1999 Apr;21(3):152-6. Publication Types: Review, Review, Tutorial.

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As disorders on the autistic spectrum are behaviorally defined, there is no medical test to diagnose autism. The purpose of a medical evaluation is to detect particular etiologies, and manifestations like clinical or subclinical epilepsy or behavior problems that might mandate pharmacologic intervention. Defining a unique syndrome or genetic etiology may benefit other family members, although, currently, specific causes are detectable in only a small minority of individuals on the autistic spectrum. The paper lists elements of the history, examination, and laboratory testing most likely to be informative in clinical practice. Ordering large numbers of tests in the absence of a specific clinical indication is not recommended because it is invasive, wasteful and unlikely to generate useful data. This is not true, of course, in the context of a hypothesis-driven, approved research protocol where collecting standardized data and applying the most up-to-date research technologies is appropriate.

6.149. Clark, T., Feehan, C., Tinline, C., Vostanis, P. "Autistic symptoms in children with attention deficit-hyperactivity disorder." *Eur Child Adolesc Psychiatry* 1999 Mar;8(1):50-5.

Parkview Clinic, Moseley, Birmingham, United Kingdom.

Children with the syndrome of disorders of attention, motor control and perception (DAMP) invariably fill diagnostic criteria for attention deficit hyperactivity disorder (ADHD) and commonly have symptoms of autistic spectrum disorders. This study estimates the rate of autistic symptoms in a sample of children with ADHD by using the parent-rated Autism Criteria Checklist. A high proportion of parents (between 65-80%) reported significant difficulties in social interaction (particularly in empathy and peer relationships), and communication (particularly in imaginative ability, nonverbal communication and maintaining conversation). The nature and relationship between ADHD and pervasive developmental disorders is considered, as well as implications for assessment, diagnosis and treatment.

6.150. Mouridsen, S.E., Rich, B., Isager, T. "Psychiatric morbidity in disintegrative psychosis and infantile autism: A long-term follow-up study." *Psychopathology* 1999 Jul-Aug;32(4):177-83.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

In order to study the validity of disintegrative psychosis (DP), the authors compared 13 patients given this diagnosis in childhood with a control group of 39 patients with infantile autism (IA) matched for sex, age, IQ and social class on measures of psychiatric morbidity. Almost the same proportion of the two groups had been admitted to a psychiatric hospital during a 22-year follow-up period. However, there was a slight tendency (statistically nonsignificant) for the DP group to utilize the psychiatric health care system more frequently than the IA group. They had more admissions and stayed longer in hospital than patients with IA suggesting that they had more psychiatric symptoms than the IA group. The original IA diagnoses were confirmed fairly consistently during the follow-up period,

while the DP group was given more heterogeneous diagnoses. No diagnosis of schizophrenia was made in either group.

6.151. Hobson, R.P., Lee, A. "Imitation and identification in autism." *J Child Psychol Psychiatry* 1999 May;40(4):649-59.

Tavistock Clinic and University College, London, UK.

This study was designed to test the prediction that adolescents with autism would have specific limitations in imitating the "style" of another person's actions. In a series of original tasks that tested the delayed imitation of novel nonsymbolic actions, 16 participants with autism and 16 nonautistic participants group-matched for age and verbal ability were proficient in copying goal-directed actions, but in 3 out of 4 tasks, strikingly fewer participants with autism imitated with style with which the demonstrator executed the actions. An additional finding was that on 2 conditions that involved copying self-orientated actions, only 5 of the participants with autism but 15 of the 16 nonautistic participants spontaneously adopted the orientation-to-self on at least 1 occasion. The results are discussed with reference to theories concerning imitation deficits in autism, and with regard to the proposal that autism involves an impairment in intersubjective contact between affected individuals and others (Hobson, 1989, 1993; Rogers & Pennington, 1991).

6.152. Rutter, M., Andersen-Wood, L., Beckett, C., Bredenkamp, D., Castle, J., Groothues, C., Kreppner, J., Keaveney, L., Lord, C., O'Connor, T.G. "Quasi-autistic patterns following severe early global privation. English and Romanian Adoptees (ERA) Study Team." *J Child Psychol Psychiatry* 1999 May;40(4):537-49.

MRC Child Psychiatry Unit and Social Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK.

Six per cent of child in a sample of 111 children who were adopted into U.K. families from Romania, and who were systematically assessed at the ages of 4 and 6 years, showed autistic-like patterns of behaviour. A further 6% showed milder (usually isolated) autistic features. Such autistic characteristics were not found in a similarly studied sample of 52 children adopted in the first 6 months of life within the U.K. The children from Romania with autistic patterns showed clinical features closely similar to "ordinary" autism at 4 years but they differed with respect to the improvement seen by age 6 years, to an equal sex ratio, and to a normal head circumference. The children from Romania with autistic features tended to differ from the other Romanian adoptees with respect to a greater degree of cognitive impairment and a longer duration of severe psychological privation.

6.153. Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C. "Social intelligence in the normal and autistic brain: an fMRI study." *Eur J Neurosci* 1999 Jun;11(6):1891-8.

Departments of Experimental Psychology and Psychiatry, University of Cambridge, UK. sb205@cus.cam.ac.uk

There is increasing support for the existence of 'social intelligence' [Humphrey (1984) *Consciousness Regained*], independent of general intelligence. Brothers et al. 1990) *J. Cog. Neurosci.*, 4, 107-118] proposed a network of neural regions that comprise the 'social brain': the orbito-frontal cortex (OFC), superior temporal gyrus (STG) and amygdala. We tested Brothers' theory by examining both normal subjects as well as patients with high-functioning autism or Asperger syndrome (AS), who are well known to have deficits in social intelligence, and perhaps deficits in amygdala function [Bauman & Kemper (1988) *J. Neuropath. Exp. Neurol.*, 47, 369]. We used a test of judging from the expressions of another person's eyes what that other person might be thinking or feeling. Using functional magnetic resonance imaging (fMRI) we confirmed Brothers' prediction that the STG and amygdala show increased activation when using social intelligence. Some areas of the prefrontal cortex also showed activation. In contrast, patients with autism or AS activated the fronto-temporal regions but not the amygdala when making mentalistic inferences from the eyes. These results provide support for the social brain theory of normal function, and the amygdala theory of autism.

6.154. Charman, T. "Autism and the pervasive developmental disorders." *Curr Opin Neurol* 1999 Apr;12(2):155-9. Publication Types: Review, Review Literature.

Behavioural Sciences Unit, Institute of Child Health, London, UK. t.charman@ich.ucl.ac.uk

Our understanding of childhood autism and the related pervasive developmental disorders continues to advance in many areas. Nevertheless, the heterogeneity of phenotypic expression presents many challenges, not least to efforts to ascertain the prevalence of the disorders. There is now wide agreement on, and reliable application of, the diagnostic criteria for childhood autism, but there is less agreement on and less reliable application of the criteria for the related disorders atypical autism, pervasive developmental disorder-unspecified and Asperger's syndrome. Evidence about genetic associations indicates that several genes are involved in creating susceptibility to the disorder, and the first steps to identify susceptibility loci have begun. Neuroanatomical models have yet to receive consistent support but early signs of promising advances have been made in pharmacological interventions, and adequate evaluation of behavioural intervention programmes is now underway.

6.155. Ottem, E. "The structures of the WISC-R subtests: a comparison of the IQ-profiles of reading impaired and autistic subjects." *Scand J Psychol* 1999 Mar;40(1):1-9.

National Centre for Logopedics, Oslo, Norway.

The present paper is an analysis of the WISC-R test profiles of reading impaired subjects and autistic subjects. It is argued that well-known classification systems such as Bannatyne's categories (1974) and Kaufman's factors (1975) cannot explain differences in the peaks and troughs across the two populations. A new classification system is then developed. The 11 different WISC-R subtests are characterised in terms

of a combination of three modes of cognitive functioning: a knowledge mode (declarative-procedural), a processing mode (transformation-preservation of information), and a verbal-nonverbal mode (verbal-nonverbal-processing). When reanalysed within this reference frame, the IQ profiles of reading impaired subjects (N = 114) and autistic subjects (data from 12 studies reviewed by Happe, 1994) were similar regarding differences in the verbal-nonverbal dimension. However, the IQ profiles showed an opposite pattern in the declarative-procedural dimension, and an opposite pattern in the preservation-transformation dimension. Thus, the new classification system allows one to interpret the IQ-profiles of both groups within a single and coherent reference frame.

6.156. Jan, M.M., Dooley, J.M., Gordon, K.E. "Male Rett syndrome variant: application of diagnostic criteria." *Pediatr Neurol* 1999 Mar;20(3):238-40. Publication Types: Review, Review of Reported Cases.

Department of Pediatrics (Neurology), King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Classic Rett syndrome (RS) has been described in females only. Although an X chromosome origin is probable, it has not been substantiated. It is possible, therefore, that RS could occur in males. The authors describe a male with RS and review all the reported cases involving male patients. The authors compare their patient to the other patients and examine the applicability of the classic RS diagnostic criteria to this variant. To date, nine male patients with RS have been reported. The authors describe an additional male who met seven of nine necessary criteria and six of eight supportive criteria as defined by the RS Diagnostic Criteria Work Group. When the authors applied these criteria to the other nine reported patients, many necessary inclusion criteria were not met despite the absence of exclusion criteria. The supportive criteria were even more variable and limited in many patients. In conclusion, males with RS appear to represent a heterogeneous phenotype, with clinical features that may meet many but not all of the necessary diagnostic criteria of classic RS. Less restrictive criteria are needed to include this variant, which should be considered when evaluating males with idiopathic developmental regression, autistic features, and loss of hand function.

6.157. Stone, W.L., Lee, E.B., Ashford, L., Brissie, J., Hepburn, S.L., Coonrod, E.E., Weiss, B.H. "Can autism be diagnosed accurately in children under 3 years?" *J Child Psychol Psychiatry* 1999 Feb;40(2):219-26.

Vanderbilt University School of Medicine, Nashville, USA.

This study investigated the reliability and stability of an autism diagnosis in children under 3 years of age who received independent diagnostic evaluations from two clinicians during two consecutive yearly evaluations. Strong evidence for the reliability and stability of the diagnosis was obtained. Diagnostic agreement between clinicians was higher for the broader discrimination of autism spectrum vs. no autism

spectrum than for the more specific discrimination of autism vs. PDD-NOS. The diagnosis of autism at age 2 was more stable than the diagnosis of PDD-NOS at the same age. Social deficits and delays in spoken language were the most prominent DSM-IV characteristics evidenced by very young children with autism.

6.158. Muller, R.A., Behen, M.E., Rothermel, R.D., Chugani, D.C., Muzik, O., Mangner, T.J., Chugani, H.T. "Brain mapping of language and auditory perception in high-functioning autistic adults: a PET study." *J Autism Dev Disord* 1999 Feb;29(1):19-31. Publication Types: Clinical Trial, Controlled Clinical Trial.

Department of Pediatrics, Wayne State University Medical Center, Detroit, Michigan, USA. AMUELLER@UCSD.EDU

We examined the brain organization for language and auditory functions in five high-functioning autistic and five normal adults, using [15O]-water positron emission tomography (PET). Cerebral blood flow was studied for rest, listening to tones, and listening to, repeating, and generating sentences. The autism group (compared to the control group) showed (a) reversed hemispheric dominance during verbal auditory stimulation; (b) a trend towards reduced activation of auditory cortex during acoustic stimulation; and (c) reduced cerebellar activation during nonverbal auditory perception and possibly expressive language. These results are compatible with findings of cerebellar anomalies and may suggest a tendency towards atypical dominance for language in autism.

6.159. Veenstra-VanderWeele, J., Gonen, D., Leventhal, B.L., Cook, E.H. Jr. "Mutation screening of the UBE3A/E6-AP gene in autistic disorder." *Mol Psychiatry* 1999 Jan;4(1):64-7.

Department of Psychiatry, University of Chicago, Illinois 60637, USA.

Previous reports of individuals with autistic disorder with maternal duplications of 15q11-q13, the Prader-Willi/Angelman syndrome region, suggest this area as a source of candidate genes in autistic disorder. Maternal truncation mutations in UBE3A, which encodes for E6-AP ubiquitin-protein ligase, have been shown to cause Angelman syndrome, which can also result from the absence of maternal chromosomal material from this region. Despite showing no evidence for imprinting in other tissues, this gene was recently discovered to be preferentially maternally expressed in human brain and expressed solely from the murine maternal chromosome in the hippocampus and cerebellar Purkinje cells, regions implicated in the neuropathology of autism. Based on this evidence, the coding region and a putative promoter region were sequenced in ten autistic subjects. Several polymorphisms were detected, but no evidence was found for a functional mutation. Evidence for likely altered regulation of UBE3A expression in maternal 15q11-q13 duplications suggests further investigation of the regulatory regions of this gene in autistic disorder.

6.160. Ryu, Y.H., Lee, J.D., Yoon, P.H., Kim, D.I., Lee, H.B., Shin, Y.J. "Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging." *Eur J Nucl Med* 1999 Mar;26(3):253-9.

Division of Nuclear Medicine, Department of Diagnostic Radiology, Yonsei University College of Medicine, Seoul, Korea.

The neuro-anatomical substrate of autism has been the subject of detailed investigation. Because previous studies have not demonstrated consistent and specific neuro-imaging findings in autism and most such studies have been performed in adults and school-aged children, we performed a retrospective review in young children in search of common functional and anatomical abnormalities with brain single-photon emission tomography (SPET) using technetium-99m ethyl cysteinate dimer (ECD) and correlative magnetic resonance imaging (MRI). The patient population was composed of 23 children aged 28-92 months (mean: 54 months) who met the diagnostic criteria of autism as defined in the DSM-IV and CARS. Brain SPET was performed after intravenous injection of 185-370 MBq of 99mTc-ECD using a brain-dedicated annular crystal gamma camera. MRI was performed in all patients, including T1, T2 axial and T1 sagittal sequences. SPET data were assessed visually. Twenty patients had abnormal SPET scans revealing focal areas of decreased perfusion. Decreased perfusion of the cerebellar hemisphere (20/23), thalami (19/23), basal ganglia (5/23) and posterior parietal (10/23) and temporal (7/23) areas were noted on brain SPET. By contrast all patients had normal MRI findings without evidence of abnormalities of the cerebellar vermis, cerebellar hemisphere, thalami, basal ganglia or parietotemporal cortex. In conclusion, extensive perfusion impairments involving the cerebellum, thalami and parietal cortex were found in this study. SPET may be more sensitive in reflecting the pathophysiology of autism than MRI. However, further studies are necessary to determine the significance of thalamic and parietal perfusion impairment in autism.

6.161. Humphries, J. "Autism: recognising the signs in young children." *Prof Care Mother Child* 1998;8(5):127-30. Publication Types: Review, Review, Tutorial.

Department of Primary and Community Nursing, University of Central Lancashire, Preston.

Autism is an organic disorder affecting several areas of a child's development. Autism is present from birth, or very soon after, but the nature of the disorder can mean that diagnosis is delayed for months for years. Early intervention can improve long-term function and help the families. Babies with autism may display characteristic features of gaze, hearing, social development and play. Nurses working with babies and young children are in a prime position to recognise these characteristics and refer the family for specialised assessment. Learning disabilities may or may not be present in children with autism. Always listen to the parents. They often suspect something is wrong even though they may not be able to be precise.

6.162. Eisenmajer, R., Prior, M., Leekam, S., Wing, L., Ong, B., Gould, J., Welham, M. "Delayed language onset as a predictor of clinical symptoms in pervasive developmental disorders." *J Autism Dev Disord* 1998 Dec;28(6):527-33.

School of Psychology, La Trobe University, Bundoora, Victoria, Australia.

DSM-IV states that Asperger Disorder may be distinguished from Autistic Disorder by a lack of a delay in early language development. The aim of this study was to establish whether the presence or absence of early language delay would predict autistic symptomatology in children diagnosed with a PDD/autism spectrum disorder. Forty-six language-delayed and 62 normal language onset individuals (M age 11 years) were compared on ICD-10 research criteria and DSM-IV criteria, receptive language, and developmental history variables. Retrospective data were also obtained to determine whether language onset predicted autism symptomatology when young (<6 years). We found that early language delay predicts more autistic symptomatology when young, but not at an older age. Early language delay is also associated with developmental motor milestone delays and lower receptive language abilities. The results question the use of early language delay as a valid discriminating variable between PDD subgroups.

6.163. Patzold, L.M., Richdale, A.L., Tonge, B.J. "An investigation into sleep characteristics of children with autism and Asperger's Disorder." *J Paediatr Child Health* 1998 Dec;34(6):528-33.

Department of Psychology and Intellectual Disability Studies, RMIT University, Bundoora, Victoria, Australia.

OBJECTIVE: The aim of the study was to investigate the specificity of sleep problems in children with autism and further explore the currently unclear association between sleep problems and daytime behaviour. **METHODOLOGY:** The Pervasive Developmental Disorder (PDD) group consisted of 31 children with autism and 7 children with Asperger's Disorder ranging in age from 44 to 152 months. The control group consisted of 36 children ranging in age from 63 to 171 months. The children were matched on age and gender, and group-matched on IQ level. A sleep diary was completed by parents over a 2-week period, in addition to several behaviour questionnaires. **RESULTS:** Results showed that children in the PDD group exhibited qualitatively and quantitatively different sleep patterns to nonautistic control children. **CONCLUSIONS:** The findings were discussed in light of current literature concerning circadian rhythm dysfunction, social difficulties, and abnormal melatonin levels in children with autism.

6.164. Deb, S., Thompson, B. "Neuroimaging in autism." *Br J Psychiatry* 1998 Oct;173:299-302. Publication Types: Review, Review Literature.

Department of Psychological Medicine, University of Wales College of Medicine, Cardiff. deb@cardiff.ac.uk

BACKGROUND: Childhood autism is a developmental disorder with distinctive clinical features and characteristic cognitive deficits. Neuroimaging techniques have been extensively used in the study of autism and related disorders. **METHOD:** Recent important literature reported on structural and functional neuroimaging in autism was reviewed and discussed in the context of other neurobiological research findings. **RESULTS:** Various abnormalities of brain structure and function have been proposed, but no focal defect has been reliably demonstrated. Important findings, so far, include increased brain volume, structural abnormality in frontal lobe and corpus callosum in a proportion of autistic individuals. Functional neuroimaging findings emphasised the imbalance in inter-regional and inter-hemispheric brain metabolism and blood flow as well as abnormality in the anterior cingulate gyrus. **CONCLUSION:** The research to date has been hindered by methodological difficulties. However, hypothesis-driven research, particularly involving activation studies and neurotransmitter/neuroreceptor activities, using functional neuroimaging will be very useful in unravelling the enigma associated with this intriguing and distressing condition.

6.165. Brasic, J.R., Barnett, J.Y., Sheitman, B.B., Lafargue, R.T., Ahn, S.C. "Clinical assessment of adventitious movements." *Psychol Rep* 1998 Dec;83(3 Pt 1):739-50.

Bellevue Hospital Center, New York University School of Medicine, New York 10016-6481, USA. brasij01@popmail.med.nyu.edu

Many procedures with variable validity and reliability have been developed in research settings to evaluate adventitious movements and related phenomena in specific populations, e.g., people with schizophrenia treated with dopamine antagonists, but these only provide global assessments or rate specific movements. A battery for rating individuals with possible movements disorders in a comprehensive way in clinical settings is needed so a protocol to assess briefly and thoroughly potential movement disorders was videotaped for five prepubertal boys with autistic disorder and severe mental retardation in a clinical trial. Utilizing a Movement Assessment Battery, four raters independently scored videotapes of 10-16 movements assessments of each of the five subjects. Experienced raters attained agreement of 59% to 100% on ratings of tardive dyskinesia and 48% to 100% on tics. Hindrances to reliability included poor quality of some tapes, high activity of subjects, and fatigue of raters.

6.166. Saitoh, O., Courchesne, E. "Magnetic resonance imaging study of the brain in autism." *Psychiatry Clin Neurosci* 1998 Dec;52 Suppl:S219-22. Publication Types: Review, Review, Tutorial.

Department of Neuropsychiatry, Faculty of Medicine Toyama Medical and Pharmaceutical University, Japan.

Autism is a neuropsychiatric disorder of social, cognitive, and language development. Cerebellar abnormality in autism has been shown consistently from autopsy and magnetic resonance image (MRI) studies. A new MRI study with careful

methodologic designs identified two subgroups of autistic patients: hypoplasia and hyperplasia of cerebellar vermal lobules VI-VII. The existence of these two subtypes was also supported via the meta-analysis of data from separate research groups. In addition to the cerebellar abnormality, recent MRI studies in autism demonstrated abnormalities in the parietal lobe and the posterior subregions of the corpus callosum where parietal cortical fibers are concentrated. Furthermore, neurobehavioral correlates of cerebellar and parietal abnormalities have also been investigated. In contrast, there is a lack of significant difference in the cross-sectional size of the posterior hippocampal formation between autistic and normal subjects, which is discrepant with predictions based on some autopsy studies.

6.167. De Giacomo, A., Fombonne, E. "Parental recognition of developmental abnormalities in autism." *Eur Child Adolesc Psychiatry* 1998 Sep;7(3):131-6.

Instituto di Clinica delle Malattie Nervose e Mentali, Bari, Italy.

In order to identify factors associated with the early detection and referral of children with pervasive developmental disorders, a sample of 82 consecutive referrals to an outpatient diagnostic service was studied. All children were thoroughly assessed with the Autism Diagnostic Interview (ADI), standardized psychological tests and direct observations. Data from the ADI on the first symptoms to arouse parental concern and on the first professional advice sought were analyzed. The mean age of children was 19.1 months (SD = 9.4) when the parents first became concerned, and the first professional advice was sought when children were 24.1 months old (SD = 11.7). The most common parental concerns were for speech and language development, followed by abnormal socio-emotional response, and medical problem or delay in milestone. In both bivariate and multiple regression analyses, the mean age of children at first parental concern and professional advice was significantly lower in the presence of mental retardation in the child, of an older sibling in the family, and of first parental concerns for medical problem/delay in milestone. More specific autistic behaviours, child's gender, social class and place of residence did not influence the age of recognition of the disorder in this sample. Health visitors and general practitioners were the first professionals contacted by parents. The implications of these findings for early detection and diagnosis of autism are discussed.

6.168. Maestrini, E., Marlow, A.J., Weeks, D.E., Monaco, A.P. "Molecular genetic investigations of autism." *J Autism Dev Disord* 1998 Oct;28(5):427-37. Publication Types: Review, Review, Tutorial.

Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom.

Genetic factors are likely to play a major role in the etiology of autism. The genetics of the disorder is however complex, probably involving the action of several genes. In an attempt to identify autism susceptibility loci we are currently undertaking a systematic screening of the whole human

genome using multiplex families. We describe the resources and the methods needed to achieve such a task, including extensive collection of family data, semiautomated genotyping technology, and specialized statistical approaches for linkage analysis of complex traits.

6.169. Teitelbaum, P., Teitelbaum, O., Nye, J., Fryman, J., Maurer, R.G. **"Movement analysis in infancy may be useful for early diagnosis of autism."** *Proc Natl Acad Sci U S A* 1998 Nov 10;95(23):13982-7.

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All of the 17 autistic children studied in the present paper showed disturbances of movement that with our methods could be detected clearly at the age of 4-6 months, and

sometimes even at birth. We used the Eshkol-Wachman Movement Analysis System in combination with still-frame videodisc analysis to study videos obtained from parents of children who had been diagnosed as autistic by conventional methods, usually around 3 years old. The videos showed their behaviors when they were infants, long before they had been diagnosed as autistic. The movement disorders varied from child to child. Disturbances were revealed in the shape of the mouth and in some or all of the milestones of development, including, lying, righting, sitting, crawling, and walking. Our findings support the view that movement disturbances play an intrinsic part in the phenomenon of autism, that they are present at birth, and that they can be used to diagnose the presence of autism in the first few months of life. They indicate the need for the development of methods of therapy to be applied from the first few months of life in autism.

MISCELLANEOUS

7.1. Pletnikov, M.V., Rubin, S.A., Moran, T.H., Carbone, K.M. "Exploring the cerebellum with a new tool: neonatal Borna disease virus (BDV) infection of the rat's brain." *Cerebellum*. 2003;2(1):62-70. Publication Types: Review, Review, Academic.

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Cerebellar pathology has been associated with a number of developmental behavioral disorders, including autism spectrum disorders. Despite the fact that perinatal virus infections have been implicated in neurodevelopmental damage, few animal models have been developed to study the pathogenesis involved. One of the most interesting in vivo models of virus-induced cerebellar damage is the neonatal Borna disease virus (BDV) infection of the rat brain. The present review describes molecular, cellular, neuroanatomical, neurochemical and behavioral features of the BDV model and also provides a basis for a new understanding of the pathogenic mechanisms of cerebellar malformation and associated behavioral deficits.

7.2. Frenkel, L.D., Nielsen, K. "Immunization issues for the 21st century." *Ann Allergy Asthma Immunol*. 2003 Jun;90(6 Suppl 3):45-52. Publication Types: Review, Review, Tutorial.

Department of Pediatrics University of Illinois, College of Medicine at Rockford, Rockford, Illinois 61107, USA. lfrenkel@uic.edu

OBJECTIVE: Review and discuss major issues of vaccination and immunization. The development and application of vaccination and immunization is one of the most remarkable successes of the 20th century. This is true both in the United States and worldwide. In the United States, a number of vaccine-preventable diseases have been all but eliminated through the development of a recommended childhood immunization schedule by governmental and nongovernmental organizations, education of providers about these recommendations, and enforcement of these recommendations by school and day care entry mandates. Despite these successes, vaccine-preventable diseases continue to occur, in part because of missed opportunities by health care providers, antivaccine forces empowered by misguided mass media, and parental ignorance. Important aspects of the 2002 recommended childhood immunization schedule are reviewed, including: birth dose hepatitis B, diphtheria underimmunization and tetanus overimmunization, increasing pertussis disease, the success of conjugate vaccines, the change in poliovirus vaccines, measles vaccine and autism, the safety of varicella vaccine, and adult vaccination recommendations. Finally, future prospects for vaccination and immunization are discussed, including: combination vaccines, vaccines against new diseases such as rotavirus, new routes of delivery of immunizing agents, the use of computerized vaccine registries to prevent missed opportunities, and vaccines against bioterrorism agents. **CONCLUSIONS:** A careful analysis of risk and benefit suggests that the benefit of vaccination far outweighs the risks from the utilization of immunizing agents.

Vaccination delayed may be protection denied. The bottom line is that vaccines are good and disease is bad.

7.3. Vincent, A., Dalton, P., Clover, L., Palace, J., Lang, B. "Antibodies to neuronal targets in neurological and psychiatric diseases." *Ann N Y Acad Sci*. 2003 May;992:48-55. Publication Types: Review, Review, Tutorial.

Neurosciences Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK.

The role of antibodies to specific neuronal and muscle ion channels in the etiology of neuromuscular transmission disorders is now well accepted. In addition, maternal antibodies can cross the placenta and cause neonatal disease or even alter the development of the infant, raising the possibility that some neurodevelopmental conditions could be caused by maternal antibodies. Voltage-gated ion channels are expressed in the brain as well as at the neuromuscular junction, and in recent years it has become clear that antibodies to some central nervous system (CNS) channels can be associated with CNS disease. This review highlights features of these conditions, preliminary investigations into neurodevelopmental disorders, and areas for further study.

7.4. Geier, M.R., Geier, D.A. "Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication." *Exp Biol Med (Maywood)*. 2003 Jun;228(6):660-4.

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We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk [RR] = 6.0), mental retardation (RR = 6.1), and speech disorders (RR = 2.2) after thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (1.7) and speech disorders (2.3) were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP (2.4 +/- 3.2 years old) and thimerosal-free DTaP (2.1 +/- 2.8 years old) vaccinations. Acute control adverse reactions such as deaths (RR = 1.0), vasculitis (RR = 1.2), seizures (RR = 1.6), ED visits (RR = 1.4), total adverse reactions (RR = 1.4), and gastroenteritis (RR = 1.1) were reported similarly after thimerosal-containing and thimerosal-free DTaP vaccines. An

association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted to confirm and extend this study.

7.5. Eriksson, K., Kylläinen, A., Hirvonen, K., Nieminen, P., Koivikko, M. "Visual agnosia in a child with non-lesional occipito-temporal CSWS." *Brain Dev.* 2003 Jun;25(4):262-7.

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In this paper we describe a case of severe visual agnosia in a child with an electrophysiological pattern of continuous spike-wave discharges in slow sleep (CSWS) in the occipito-temporal regions. The neuropsychological spectrum related to this phenomenon is discussed. Published paediatric reports associate visual agnosia (i.e. an inability to recognize objects without impairment of visual acuity) mainly with symptomatic occipito-temporal aetiology (e.g. cortical dysplasia, vascular insults) and other neurological symptoms (e.g. autism). We describe a detailed 2 year electrophysiological and neuropsychological follow-up of an 8-year-old boy with sporadic seizures, occipito-temporal CSWS and visual agnosia. The growth and neurological development of the child had been considered as normal, neurological examination did not reveal any focal signs, visual acuity was intact and MRI was normal. First EEG and six consecutive 24 h video EEG recordings during the follow-up of 22 months showed continuous spike-and-wave activity covering over 85% of the non-REM sleep. According to structured neuropsychological tests (Wechsler Intelligence Scale for Children—Third Edition, A Developmental Neuropsychological Assessment (NEPSY), Test of Visual-Perceptual Skills, Corsi block, Hooper Visual Organization Test) the boy had normal verbal intelligence but major deficits in visual perception, especially in object recognition, impaired shape discrimination and detection, and poor copying skills. Attention and executive functions were intact. There were no difficulties in short- or long-term memory. Verbal cues and naming the objects improved visual memory. Tracing the objects with a finger or by moving the head improved object recognition. Currently the boy attends a special school with a rehabilitation plan including neuropsychological and occupational therapies. This case adds a new facet to the spectrum of neuropsychological deficits in children with CSWS. Sleep EEG should be included in the etiological studies of children with specific neuropsychological problems and detailed neuropsychological assessment is needed for diagnostic and rehabilitation purposes.

7.6. Martin, I., McDonald, S. "Weak coherence, no theory of mind, or executive dysfunction? Solving the puzzle of pragmatic language disorders." *Brain Lang.* 2003 Jun;85(3):451-66. Publication Types: Review, Review, Academic.

School of Psychology, University of New South Wales, Sydney 2052, Australia.

Deficits in pragmatic language ability are common to a number of clinical populations, for example, right-hemisphere damage (RHD), Autism and traumatic brain injury (TBI). In these individuals the basic structural components of language may be intact, but the ability to use language to engage socially is impaired. Despite the nature of these difficulties being well documented, exactly what causes these difficulties is less clear. Furthermore, the current status of causal explanations for pragmatic difficulties across these populations is divergent and sometimes contradictory. This paper explores the empirical validity of three theories that attempt to explain pragmatic language impairment. It is recommended that a new, more convergent approach to investigating the causes of pragmatic language disability be adopted.

7.7. Owens, J.A., Rosen, C.L., Mindell, J.A. "Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians." *Pediatrics.* 2003 May;111(5 Pt 1):e628-35. Publication Types: Multicenter Study.

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OBJECTIVES: To examine clinical practice patterns, beliefs, and attitudes regarding the use of both nonprescription and prescription medications by community-based pediatricians for children with significant difficulties in initiating and/or maintaining sleep. **METHODS:** A survey was mailed to 3424 American Academy of Pediatrics members in 6 US cities. **RESULTS:** The final sample (n = 671) consisted of practitioners who identified themselves as primary care pediatricians. Three percent +/- 7% of visits in the respondents' practices were for pediatric insomnia, although there was a wide range in the numbers of children identified during a typical 6-month practice period. More than 75% of practitioners had recommended nonprescription medications, and >50% had prescribed a sleep medication. Specific clinical circumstances in which medications were most commonly used were acute pain and travel, followed by children with special needs (mental retardation, autism, and attention-deficit/hyperactivity disorder). Antihistamines were the most commonly reported nonprescription medications for sleep. Melatonin or herbal remedies had been recommended by approximately 15% of the respondents. alpha-agonists were the most frequently prescribed sleep medications (31%). The likelihood of prescribing medication for sleep was 2- to 4-fold greater in respondents who treated children with attention-deficit/hyperactivity disorder for daytime behavioral problems or nocturnal sleep problems, respectively. Practitioners expressed a range of concerns about sleep medication appropriateness, safety, tolerance, and side effects in children. **CONCLUSIONS:** The practice of prescribing or recommending sedatives and hypnotics for pediatric insomnia is common among community-based pediatricians, especially among special needs patients. An empirically based approach to the use of these medications is needed.

7.8. Roane, H.S., Fisher, W.W., McDonough, E.M. "Progressing from programmatic to discovery research: a case example with the overjustification effect." *J Appl Behav Anal.* 2003 Spring;36(1):35-46. Publication Types: Evaluation Studies.

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Scientific research progresses along planned (programmatic research) and unplanned (discovery research) paths. In the current investigation, we attempted to conduct a single-case evaluation of the overjustification effect (i.e., programmatic research). Results of the initial analysis were contrary to the overjustification hypothesis in that removal of the reward contingency produced an increase in responding. Based on this unexpected finding, we conducted subsequent analyses to further evaluate the mechanisms underlying these results (i.e., discovery research). Results of the additional analyses suggested that the reward contingency functioned as punishment (because the participant preferred the task to the rewards) and that withdrawal of the contingency produced punishment contrast.

7.9. O'Brien, E.K., Zhang, X., Nishimura, C., Tomblin, J.B., Murray, J.C. "Association of specific language impairment (SLI) to the region of 7q31." *Am J Hum Genet.* 2003 Jun;72(6):1536-43. *Epub* 2003 Apr 29.

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FOXP2 (forkhead box P2) was the first gene characterized in which a mutation affects human speech and language abilities. A common developmental language disorder, specific language impairment (SLI), affects 6%-7% of children with normal nonverbal intelligence and has evidence of a genetic basis in familial and twin studies. FOXP2 is located on chromosome 7q31, and studies of other disorders with speech and language impairment, including autism, have found linkage to this region. In the present study, samples from children with SLI and their family members were used to study linkage and association of SLI to markers within and around FOXP2, and samples from 96 probands with SLI were directly sequenced for the mutation in exon 14 of FOXP2. No mutations were found in exon 14 of FOXP2, but strong association was found to a marker within the CFTR gene and another marker on 7q31, D7S3052, both adjacent to FOXP2, suggesting that genetic factors for regulation of common language impairment reside in the vicinity of FOXP2.

7.10. Sutcliffe, J.S., Han, M.K., Amin, T., Kesterson, R.A., Nurmi, E.L. "Partial duplication of the APBA2 gene in chromosome 15q13 corresponds to duplication structures." *BMC Genomics.* 2003 Apr 29;4(1):15.

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BACKGROUND: Chromosomal abnormalities affecting human chromosome 15q11-q13 underlie multiple genomic

disorders caused by deletion, duplication and triplication of intervals in this region. These events are mediated by highly homologous segments of DNA, or duplicons, that facilitate mispairing and unequal cross-over in meiosis. The gene encoding an amyloid precursor protein-binding protein (APBA2) was previously mapped to the distal portion of the interval commonly deleted in Prader-Willi and Angelman syndromes and duplicated in cases of autism. **RESULTS:** We show that this gene actually maps to a more telomeric location and is partially duplicated within the broader region. Two highly homologous copies of an interval containing a large 5' exon and downstream sequence are located approximately 5 Mb distal to the intact locus. The duplicated copies, containing the first coding exon of APBA2, can be distinguished by single nucleotide sequence differences and are transcriptionally inactive. Adjacent to APBA2 maps a gene termed KIAA0574. The protein encoded by this gene is weakly homologous to a protein termed X123 that in turn maps adjacent to APBA1 on 9q21.12; APBA1 is highly homologous to APBA2 in the C-terminal region and is distinguished from APBA2 by the N-terminal region encoded by this duplicated exon. **CONCLUSION:** The duplication of APBA2 sequences in this region adds to a complex picture of different low copy repeats present across this region and elsewhere on the chromosome.

7.11. Starr, E., Szatmari, P., Bryson, S., Zwaigenbaum, L. "Stability and change among high-functioning children with pervasive developmental disorders: a 2-year outcome study." *J Autism Dev Disord.* 2003 Feb;33(1):15-22.

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This study prospectively compared the 2-year outcome of children diagnosed with autism or Asperger syndrome at age 6-8 years in terms of symptoms from the Autism Diagnostic Interview. Significant differences were seen in the three-domain summary scores of social interaction, communication, and repetitive activities, with the Asperger syndrome group demonstrating fewer and/or less severe symptoms at both times. There was a trend for the trajectories to come together over time on the socialization and communication domains, but not the repetitive activities domain. Differences were not attributable to IQ. Analysis of individual items indicated that the autism group improved over time on seven items and showed increased symptom severity on three items. On the other hand, the Asperger syndrome group improved on only two items and showed increased symptom severity on six items. Results suggest that the two PDD subtypes represent similar developmental trajectories, although the Asperger syndrome group maintains its advantage. Educational and clinical implications of the results are discussed.

7.12. Roizen, N.J., Patterson, D. "Down's syndrome." *Lancet.* 2003 Apr 12;361(9365):1281-9. *Comment in: Lancet.* 2003 Jul 5;362(9377):80-1. *Lancet.* 2003 Jul 5;362(9377):81. Publication Types: Review, Review, Tutorial.

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The sequencing of chromosome 21 and the use of models of Down's syndrome in mice have allowed us to relate genes and sets of genes to the neuropathogenesis of this syndrome, and to better understand its phenotype. Research in prenatal screening and diagnosis aims to find methods to identify fetuses with Down's syndrome, and reduce or eliminate the need for amniocentesis. Other areas of active research and clinical interest include the association of Down's syndrome with coeliac disease and Alzheimer's disease, and improved median age of death. Medical management of the syndrome requires an organised approach of assessment, monitoring, prevention, and vigilance. Improvements in quality of life of individuals with Down's syndrome have resulted from improvements in medical care, identification and treatment of psychiatric disorders (such as depression, disruptive behaviour disorders, and autism), and early educational interventions with support in typical educational settings. Approaches and outcomes differ throughout the world.

7.13. Chandler, K.E., Moffett, M., Clayton-Smith, J., Baker, G.A. "Neuropsychological assessment of a group of UK patients with Cohen syndrome." *Neuropediatr.cs.* 2003 Feb;34(1):7-13.

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Cohen syndrome is a rare autosomal recessive syndrome with a distinctive clinical phenotype that includes mental retardation and a characteristic sociable disposition. Variability in the level of learning disability and the behavioural phenotype is seen in the published literature. In a cohort of Finnish Cohen syndrome patients, severe mental retardation and non-maladaptive behaviour were described. Outside of Finland, autistic-spectrum behaviour has been reported in a few isolated Cohen syndrome patients but in a recent UK study was found to be highly prevalent. We report the results of neuropsychological studies in a group of 16 genetically heterogeneous patients, all with the characteristic clinical features of Cohen syndrome. Of the 9 patients who underwent formal neuropsychological testing, all but one was functioning in the severely mentally impaired range. Of the remaining patients, 3 were below the age of formal testing and 4 had such profound learning and behavioural problems that they were deemed unable to participate in testing. Mild maladaptive behaviour was observed in 13 patients and 3 were documented as having significant maladaptive behaviour. In contrast to the Finnish group of Cohen syndrome patients, this UK study identifies significant neuropsychological impairment combined with maladaptive behaviour as a characteristic of Cohen syndrome. Although autistic-type behaviour was observed, an increased prevalence of autism in Cohen syndrome was not confirmed.

7.14. Scherer, S.W., Cheung, J., MacDonald, J.R., Osborne, L.R., Nakabayashi, K., Herbrick, J.A., Carson, A.R., Parker-Katirae, L., Skaug, J., Khaja, R., Zhang, J., Hudek, A.K., Li, M., Haddad, M., Duggan, G.E., Fernandez, B.A., Kanematsu, E., Gentles, S., Christopoulos, C.C., Choufani, S., Kwasnicka,

D., Zheng, X.H., Lai, Z., Nusskern, D., Zhang, Q., Gu, Z., Lu, F., Zeeman, S., Nowaczyk, M.J., Teshima, I., Chitayat, D., Shuman, C., Weksberg, R., Zackai, E.H., Grebe, T.A., Cox, S.R., Kirkpatrick, S.J., Rahman, N., Friedman, J.M., Heng, H.H., Pelicci, P.G., Lo-Coco, F., Belloni, E., Shaffer, L.G., Pober, B., Morton, C.C., Gusella, J.F., Bruns, G.A., Korf, B.R., Quade, B.J., Ligon, A.H., Ferguson, H., Higgins, A.W., Leach, N.T., Herrick, S.R., Lemyre, E., Farra, C.G., Kim, H.G., Summers, A.M., Gripp, K.W., Roberts, W., Szatmari, P., Winsor, E.J., Grzeschik, K.H., Teebi, A., Minassian, B.A., Kere, J., Armengol, L., Pujana, M.A., Estivill, X., Wilson, M.D., Koop, B.F., Tosi, S., Moore, G.E., Boright, A.P., Zlotorynski, E., Kerem, B., Kroisel, P.M., Petek, E., Oscier, D.G., Mould, S.J., Dohner, H., Dohner, K., Rommens, J.M., Vincent, J.B., Venter, J.C., Li, P.W., Mural, R.J., Adams, M.D., Tsui, L.C. "Human chromosome 7: DNA sequence and biology." *Science.* 2003 May 2;300(5620):767-72. *Epub* 2003 Apr 10.

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DNA sequence and annotation of the entire human chromosome 7, encompassing nearly 158 million nucleotides of DNA and 1917 gene structures, are presented. To generate a higher order description, additional structural features such as imprinted genes, fragile sites, and segmental duplications were integrated at the level of the DNA sequence with medical genetic data, including 440 chromosome rearrangement breakpoints associated with disease. This approach enabled the discovery of candidate genes for developmental diseases including autism.

7.15. Johnson, S.C. "Detecting agents." *Philos Trans R Soc Lond B Biol Sci.* 2003 Mar 29;358(1431):549-59.

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This paper reviews a recent set of behavioural studies that examine the scope and nature of the representational system underlying theory-of-mind development. Studies with typically developing infants, adults and children with autism all converge on the claim that there is a specialized input system that uses not only morphological cues, but also behavioural cues to categorize novel objects as agents. Evidence is reviewed in which 12- to 15-month-old infants treat certain non-human objects as if they have perceptual/attentional abilities, communicative abilities and goal-directed behaviour. They will follow the attentional orientation of an amorphously shaped novel object if it interacts contingently with them or with another person. They also seem to use a novel object's environmentally directed behaviour to determine its perceptual/attentional orientation and object-oriented goals. Results from adults and children with autism are strikingly similar, despite adults' contradictory beliefs about the objects in question and the failure of children with autism to ultimately develop more advanced theory-of-mind reasoning. The implications for a general theory-of-mind development are discussed.

7.16. Takaoka, K., Takata, T. "Catatonia in childhood and adolescence." *Psychiatry Clin Neurosci.* 2003 Apr;57(2):129-37. Publication Types: Review, Review, Academic.

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Child and adolescent catatonia has been poorly investigated. A literature review was undertaken to clarify phenomenology, diagnosis, etiology, and treatment as well as ethical problems of catatonia in childhood and adolescence. Although there are no accepted standardized criteria for catatonia in childhood and adolescence, catatonic features described by child psychiatrists are similar to Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV) criteria for catatonia. With respect to etiology, the motor and behavioral symptoms that are part of catatonia bear some similarities with those seen in autism. Several case reports suggest an association between catatonia and general medical conditions. Certain drugs abused by youngsters as well as prescribed medicine can induce catatonia. Regarding catatonic cases originally diagnosed as schizophrenia, it is unclear whether all of these cases should be identified as schizophrenia or whether some of them are pervasive developmental disorders that develop psychic features in adolescence. Environmental changes preceding the onset of catatonia in patients with mood disorder play a possibly important role. Examples that suggest stress-induced catatonia, although rare, also exist. A few patients exhibit features of malignant catatonia, some without taking neuroleptics and others having taken them. Benzodiazepines and electroconvulsive therapy are considered to be effective treatments for catatonic youngsters.

7.17. Ambrosini, P.J., Elia, J., Rynn, M.A. "49th Annual Meeting of the American Academy of Child & Adolescent Psychiatry. 22-27 October 2002, San Francisco, CA, USA." *Expert Opin Pharmacother.* 2003 Apr;4(4):591-4.

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The diverse programme covered recent advances in developmental neurobiology, genetics, psychotherapy and pharmacotherapy. Presentations included clinical consultation breakfasts, with experts in their specialities, clinical case conferences, media theatre events, symposia, special interest groups, workshops and poster presentations. Several awards were presented to members to acknowledge their research achievements and service to the academy, and to children in need. All the presentations were focused on keeping the clinician and the researcher up-to-date on the advancements within the field of child and adolescent psychiatry. This report will focus on the new research poster presentations, which highlight the current status of paediatric pharmacotherapy. The data will be presented within the major diagnostic groups of the affective, behavioural, anxiety and developmental, autistic and psychotic syndromes. In paediatric pharmacotherapy particularly, several agents are administered as broad spectrum pharmacotherapeutics, and therefore, are used across several disorders.

7.18. Symons, F.J., Clark, R.D., Hatton, D.D., Skinner, M., Bailey, D.B. Jr. "Self-injurious behavior in young boys with fragile X syndrome." *Am J Med Genet.* 2003 Apr 15;118A(2):115-21.

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In this study, we distributed surveys to 67 families of young boys with fragile X syndrome to determine the prevalence, onset, form, function, location, and correlates of self-injurious behavior. Fifty-five surveys were completed (82%). The mean age of the boys at the time of the survey was 80 months (range = 20-144). Self-injurious behavior (SIB) was reported for 58% of the participants with a mean age of onset of 31 months. The mean number of forms of self-injury was 2 per participant. Biting was the most commonly reported form of self-injury with the fingers and back of the hand disproportionately targeted as the most prevalent self-injury body site. There was no linear increase in risk of SIB with age past 25 months. SIB was reported as most likely to occur following the presentation of difficult task demands or changes in routine. Significant group differences were found between overall ratings of problem behavior for boys with self-injury compared to those without self-injury. Groups did not differ on measures of fragile X mental retardation protein (FMRP), autism status, adaptive behavior, or age first medicated. Results are discussed in terms of future research designed to further elucidate the behavioral phenotype of fragile X syndrome. Copyright 2003 Wiley-Liss, Inc.

7.19. Constantino, J.N., Hudziak, J.J., Todd, R.D. "Deficits in reciprocal social behavior in male twins: evidence for a genetically independent domain of psychopathology." *J Am Acad Child Adolesc Psychiatry.* 2003 Apr;42(4):458-67. Publication Types: Twin Study.

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OBJECTIVE: Previous studies have demonstrated substantial genetic influences on many child psychiatric disorders, including autism. In this study the authors attempted to quantify the degree to which genetic influences on deficits in reciprocal social behavior (a defining feature of pervasive developmental disorders) are shared with genetic influences on other domains of behavior in children. **METHOD:** Child Behavior Checklists (CBCL) and Social Responsiveness Scales (SRS) were completed for an epidemiological sample of 219 pairs of male twins. The SRS (formerly known as the Social Reciprocity Scale) is a measure of social impairment that distinguishes children with autism spectrum disorders from those with other child psychiatric disorders. **RESULTS:** Regression analysis indicated that CBCL syndromes account for 43% of the variance in SRS scores. Bivariate analyses revealed that SRS scores are affected, in part, by phenotypic influences from the CBCL Social Problem syndrome. Forty-four percent of the causal influences on SRS scores, however,

are independent from those on CBI. syndromes and are genetic in nature (90% confidence interval: 0.38-0.49). CONCLUSION: These results support the existence of a continuous distribution of deficits in reciprocal social behavior in the population, which are substantially genetically independent from other domains of child psychopathology.

7.20. Hippler, K., Klicpera, C. "A retrospective analysis of the clinical case records of 'autistic psychopaths' diagnosed by Hans Asperger and his team at the University Children's Hospital, Vienna." *Philos Trans R Soc Lond B Biol Sci.* 2003 Feb 28;358(1430):291-301.

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To date, it is questionable whether the diagnostic criteria for Asperger syndrome (AS) as stated by ICD-10 or DSM-IV still reflect Asperger's original account of 'autistic psychopathy' (AP) from the 1940s. The present study examined 74 clinical case records of children with AP diagnosed by Hans Asperger and his team at the Viennese Children's Clinic and Asperger's private practice between 1950 and 1986. The characteristic features of the children are outlined, including reasons for referral, parental background, behavioural problems, cognitive functioning, communication and interests. Results show that the patients of Asperger described in our study represent a subgroup of children with very high intellectual functioning, specific circumscribed interests and talents but impaired social, communication and motor skills. Sixty-eight percent of the sample met ICD-10 criteria for AS, while 25% fulfilled the diagnostic criteria for autism. Implications for the diagnosis of AS are discussed.

7.21. Brogan, C.A., Knussen, C. "The disclosure of a diagnosis of an autistic spectrum disorder: determinants of satisfaction in a sample of Scottish parents." *Autism.* 2003 Mar;7(1):31-46.

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Satisfaction with disclosure of the diagnosis of an autistic spectrum disorder was investigated using a self-report questionnaire completed by 126 parents. On a rating of satisfaction, 55 percent indicated that they were satisfied or very satisfied with the disclosure. Parents were more likely to be satisfied if they gave positive ratings to the manner of the professional and the quality of the information provided; if they had been given written information and the opportunity to ask questions; and if their early suspicions had been accepted by professionals. These factors were combined into a global index of satisfaction; those gaining higher scores were more likely to have been given the diagnosis of Asperger syndrome (as opposed to autism), to have had a definite diagnosis, and to have children who were not currently in an educational placement. These results underline the importance of the interaction between parent and professional during the disclosure interview.

7.22. Ferro, A. "Marcella: the transition from explosive sensoriality to the ability to think." *Psychoanal Q.* 2003 Jan;72(1):183-200.

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The author discusses an analytic case in which it was necessary to first address the patient's need for containment of her protoemotions—her sensoriality—before the analysis could proceed along more standard lines, with interpretation of the transference, work on displacement and aspects of her childhood history, and so forth. Prior to treatment, the patient had resorted to a sort of affective autism in order not to experience dangerously overwhelming emotions, and her emotional lethargy in sessions at first engendered similar feelings in the analyst, making progress impossible until a container was established for her projective identifications.

7.23. Msall, M.E., Avery, R.C., Tremont, M.R., Lima, J.C., Rogers, M.L., Hogan, D.P. "Functional disability and school activity limitations in 41,300 school-age children: relationship to medical impairments." *Pediatrics.* 2003 Mar;111(3):548-53.

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OBJECTIVE: Our purpose was to examine the contribution of medical impairments to functional disability and school activity limitations in 41,300 school-age children participating in the 1994-1995 National Health Interview Survey. METHODS: The 1994 and 1995 National Health Interview Survey and Disability Interview Supplement samples provide International Classification of Diseases, Ninth Revision medical impairment codes for children with functional limitations or school activity limitations in a nationally representative US sample. Functional limitations were distributed as follows: mobility 12.4/1000 (95% confidence interval [CI]: 11.1-13.6), self-care 8.8/1000 (95% CI: 7.7-9.8), communication 52.9/1000 (95% CI: 50.2-55.5), and learning 104.6/1000 (95% CI: 100.7-108.4). Functional disability status was classified as 4.1% mild, 5.9% major, and 1.9% multiple. School activity limitations included 4.1% needing or receiving special education, 0.7% unable to attend, and 0.9% limited attendance. We categorized International Classification of Diseases, Ninth Revision impairment codes reported in conjunction with medical usage as physical disorders (n = 1251; eg, leukemia, diabetes), asthma (n = 916), neurodevelopmental disorders (n = 802; eg, cerebral palsy, epilepsy, mental retardation, autism, blindness, deafness), and learning-behavior disorders (n = 806; eg, attention-deficit/hyperactivity disorder, learning disability, anxiety) for children with functional or school activity limitations. Of children with multiple functional disabilities, 29.9% had neurodevelopmental disorders, 27.1% had learning-behavior disorders, 18.1% had physical disorders, 4.2% had asthma, and 20.8% did not have an identified medical impairment because they had not received medical services in the past year. Among children requiring special education, physical disorders accounted for 9.4%, neurodevelopmental disorders

for 16.7%, learning and behavior disorders for 17%, asthma for 3.4%, and 53.4% did not have an identified medical impairment because they had not received medical services in the past year. **CONCLUSIONS:** Chronic health impairments, neurodevelopmental disorders, learning-behavior disorders, and functional limitations in essential activities are required to understand the complexity of disability in school-age children. A large number of children with functional disability or school activity limitations have not received ongoing medical services.

7.24. Ceccherini-Nelli, A., Crow, T.J. "Disintegration of the components of language as the path to a revision of Bleuler's and Schneider's concepts of schizophrenia. Linguistic disturbances compared with first-rank symptoms in acute psychosis." *Br J Psychiatry*. 2003 Mar;182:233-40.

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BACKGROUND: The 20th century ended without a resolution of the debate about the supremacy of Schneider's psychopathological conceptualisation of schizophrenia (the first-rank symptoms) over Bleuler's 'four As' (disorders of association and affect, ambivalence and autism). **AIMS:** To examine the relationships between linguistic deviations and symptoms in patients with acute psychosis. **METHOD:** We assessed language disturbances and first-rank symptoms with the Clinical Language Disorder Rating Scale (CLANG) in 30 consecutive patients with acute psychosis, selected for the presence of at least one active first-rank symptom, and 15 control participants with depression but no psychotic symptoms. **RESULTS:** Strong positive correlations were found between the CLANG factor 'poverty' (of speech) and first-rank delusions of control and ('delusional perceptions') between semantic/phonemic paraphasias and verbal auditory hallucinations. Language disturbances were superior to nuclear symptoms in discriminating ICD-10 schizophrenia from other psychoses. **CONCLUSIONS:** Evaluating the features of psychosis as deviations in the cerebral organisation of language paves the way to a concept of psychosis that supersedes these traditional but competing categorical concepts.

7.25. Marek, G.J., Carpenter, L.L., McDougle, C.J., Price, L.H. "Synergistic action of 5-HT_{2A} antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders." *Neuropsychopharmacology*. 2003 Feb;28(2):402-12. Publication Types: Review, Tutorial.

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Recently, the addition of drugs with prominent 5-HT(2) receptor antagonist properties (risperidone, olanzapine, mirtazapine, and mianserin) to selective serotonin reuptake inhibitors (SSRIs) has been shown to enhance therapeutic responses in patients with major depression and treatment-refractory obsessive-compulsive disorder (OCD). These 5-HT(2) antagonists may also be effective in ameliorating some symptoms associated with autism and other pervasive

developmental disorders (PDDs). At the doses used, these drugs would be expected to saturate 5-HT(2A) receptors. These findings suggest that the simultaneous blockade of 5-HT(2A) receptors and activation of an unknown constellation of other 5-HT receptors indirectly as a result of 5-HT uptake inhibition might have greater therapeutic efficacy than either action alone. Animal studies have suggested that activation of 5-HT(1A) and 5-HT(2C) receptors may counteract the effects of activating 5-HT(2A) receptors. Additional 5-HT receptors, such as the 5-HT(1B/1D/5/7) receptors, may similarly counteract the effects of 5-HT(2A) receptor activation. These clinical and preclinical observations suggest that the combination of highly selective 5-HT(2A) antagonists and SSRIs, as well as strategies to combine high-potency 5-HT(2A) receptor and 5-HT transporter blockade in a single compound, offer the potential for therapeutic advances in a number of neuropsychiatric disorders.

7.26. Strauss, D.J., Day, S.M., Shavelle, R.M., Wu, Y.W. "Remote symptomatic epilepsy: does seizure severity increase mortality?" *Neurology*. 2003 Feb 11;60(3):395-9.

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OBJECTIVE: To investigate the excess mortality due to remote symptomatic epilepsy, taking account of frequency and type of seizures. **METHODS:** The authors compared mortality in persons with (n = 8,156) and without (n = 72,526) history of epilepsy in a 1988 to 1999 California population of persons with mild developmental disabilities. Subjects had traumatic brain injury, cerebral palsy, Down syndrome, autism, or no identifiable condition. There were 506,204 person-years of data, with 1,523 deaths. Excess death rates and standardized mortality ratios were computed for the persons in the study with epilepsy, relative to those in the study without epilepsy. Controlled comparisons were made using logistic regression on person-years. **RESULTS:** Compared to subjects with no epilepsy, the excess mortality was six (deaths per 1,000 persons per year) for persons with a recent (<12 months) history of status epilepticus, five for a recent history of generalized tonic-clonic seizure, three for a recent history of nonconvulsive seizures, and less than one for a history of epilepsy but no recent events. Proportion in remission and excess mortality showed no change over the 12-year study period. **CONCLUSIONS:** Persistent seizures are associated with increased mortality in remote symptomatic epilepsy. Mortality is highest among individuals with status epilepticus or generalized convulsions.

7.27. Rastam, M., Gillberg, C., Wentz, E. "Outcome of teenage-onset anorexia nervosa in a Swedish community-based sample." *Eur Child Adolesc Psychiatry*. 2003;12 Suppl 1:178-90.

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In a prospective long-term outcome study of a representative sample of teenage-onset anorexia nervosa (AN), 51

individuals with AN, recruited after community screening, were contrasted with 51 matched comparison cases at a mean age of 24 years (10 years after AN onset). All 102 cases had been examined at age 16 and 21 years. At 24 years all probands were interviewed regarding mental and physical health, and overall outcome was assessed. Ten-year outcome of teenage-onset AN seemed to be relatively favourable in that half of all cases were free from eating disorder (ED) and other axis I disorder. There were no deaths. However, one in four in the AN group had a persisting ED, 3 of whom still had AN. Lifetime diagnoses of affective disorders and obsessive-compulsive disorder (OCD) were overrepresented in the AN group. Affective disorders coincided with the ED, and were not a problem after recovery from the ED. On the other hand, OCD, OCPD (obsessive-compulsive personality disorder), and/or autism spectrum disorder continued to characterise more than one-third of the AN cases. One in six of the AN group had persistent problems with social interaction and obsessive compulsive behaviours from childhood into early adult years. Half the AN group had a poor overall outcome. These were subjects with either persisting ED or lifelong problems with social interaction and obsessive compulsive behaviour.

7.28. Cohen, M.M. Jr. "Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth syndromes." *Am J Med Genet.* 2003 Feb 15;117C(1):49-56. Publication Types: Review, Review, Academic.

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Mental deficiency, alterations in performance, and central nervous system (CNS) abnormalities are discussed in the following overgrowth syndromes: Sotos syndrome, Weaver syndrome, Proteus syndrome, neurofibromatosis type 1, fragile X syndrome, syndromes with neonatal hypoglycemia, Simpson-Golabi-Behmel syndrome, hemihyperplasia, Sturge-Weber syndrome, Bannayan-Riley-Ruvalcaba/Cowden syndrome, macrocephaly-autism syndrome, PEHO syndrome, chromosomal syndromes, and other miscellaneous syndromes. Copyright 2003 Wiley-Liss, Inc.

7.29. Hurley, A.D., Folstein, M., Lam, N. "Patients with and without intellectual disability seeking outpatient psychiatric services: diagnoses and prescribing pattern." *J Intellect Disabil Res.* 2003 Jan;47(Pt 1):39-50.

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BACKGROUND: The present study examined the presenting problem of psychiatric outpatients, and resulting diagnostic and prescribing patterns, comparing patients with intellectual disability (ID) with non-ID (N-ID) patients seen in the same clinic. **METHODS:** This study was a retrospective medical chart review of information in the first psychiatric diagnostic evaluation for the most recent 100 adult patients with mild ID, 100 patients with moderate, severe or profound ID, and 100 matching N-ID patients. **RESULTS:** There were significant

differences in rates of medical illness, disabilities, history of marriage, children, independent living, and family history of psychiatric and neurological disorders. Individuals with ID were more likely to present with aggression, self-injurious behaviour or physical complaints, whereas N-ID subjects presented more frequently with depression and anxiety complaints. For all groups, depressive disorders were the most frequent class of diagnoses. For those with ID, antipsychotics were used in 32% of subjects, with mood stabilizers in 28% and antidepressants in 27%. The N-ID subjects were most frequently prescribed antidepressants (40%) and anxiolytics (22%). Polypharmacy did not differ significantly among groups. **CONCLUSIONS:** Psychiatric practitioners relied on the diagnostic examination to formulate their diagnosis, whereas the chief complaint reflected the view of caregivers of the subjects with ID. In contrast to previous studies, outpatient providers frequently diagnosed depression, and the prescribing pattern showed increased usage of antidepressants and mood stabilizers.

7.30. Machado, C.J., Bachevalier, J. "Non-human primate models of childhood psychopathology: the promise and the limitations." *J Child Psychol Psychiatry.* 2003 Jan;44(1):64-87. Publication Types: Review, Review, Academic.

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Although non-human primate models have been used previously to investigate the neurobiology of several sensory and cognitive developmental pathologies, they have been employed only sparingly to study the etiology of childhood psychopathologies for which deficits in social behavior and emotion regulation are major symptoms. Previous investigations of both adult human and non-human primates have indicated that primate social behavior and emotion are regulated by a complex neural network, in which the amygdala and orbital frontal cortex play major roles. Therefore, this review will provide information generated from the study of macaque monkeys regarding the timing of normal social and emotional behavior development, the normal pattern of anatomical and functional maturation of the amygdala and orbital frontal cortex, as well as information regarding the neural and behavioral effects of early perturbations of these two neural structures. We will also highlight 'critical periods' of macaque development, during which major refinements in the behavioral repertoire appear to coincide with significant neural maturation of the amygdala and/or orbital frontal cortex. The identification of these 'critical periods' may allow one to better predict the specific behavioral impairments likely to appear after neonatal damage to one or both of these neural areas at different time points during development. This experimental approach may provide a new and important way to inform and stimulate research on childhood psychopathologies, such as autism, schizophrenia and Williams syndrome, in which the development of normal social skills and emotional regulation is severely perturbed. Finally, the promise and limitations inherent to the use of non-human primate models of childhood psychopathology will be discussed.

7.31. Shannon, M., Woolf, A., Goldman, R. "Children's environmental health: one year in a pediatric environmental health specialty unit." *Ambul Pediatr.* 2003 Jan-Feb;3(1):53-6.

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BACKGROUND/OBJECTIVE: As a result of an increasing desire among physicians and parents for clinical centers that can evaluate children with known or suspected exposures to environmental toxicants, a network of federally funded "pediatric environmental health specialty units" has recently been created. This descriptive study profiles the children seen in one unit of this program. **SETTING:** A New England, university-affiliated Pediatric Environmental Health Center (PEHC). **METHODS:** Review and analysis of all children seen in the PEHC in calendar year 1999. **RESULTS:** Over the course of the year, 281 children made 863 visits to the PEHC. Presenting complaints fell into 4 major categories: new visit for management of lead intoxication (n = 248), return visit for management of lead intoxication (n = 569), new visit for evaluation of exposure to an environmental toxicant other than lead (n = 33), and return visit for the management of exposure to a non-lead toxicant (n = 13). Among those children with new visits for a non-lead toxicant, the most common chief complaints were exposure to solvent-contaminated water (n = 7), pesticide exposure (n = 6), illness associated with proximity to a hazardous waste site (n = 6), autism from suspected mercury intoxication (n = 4), and evaluation of school-induced, building-related illness ("sick school syndrome")(n = 4). Eleven children had autism or pervasive developmental delay. Families traveled distances as great as 450 kilometers for evaluation by a pediatric environmental health clinical specialist. Every child was evaluated by a pediatrician with subspecialty training in medical toxicology. Environmental investigation of air, water, paint, dust, or land was conducted for all except 4 children (all foreign-born adoptees). Therapeutic interventions included chelation therapy, relocation to a safe environment, removal from school, and termination of chelation therapy that had been initiated by another practitioner. Third-party payors provided full reimbursement for all visits. **CONCLUSIONS:** The chief complaints of the children brought to pediatric environmental health specialty units are diverse, involving exposures to a wide range of toxicants from all environmental media (air, water, soil, and food). Parents desiring such an evaluation must often travel extensive distances, suggesting the need for a broader network of such centers. Third-party payors and health maintenance organizations are willing to provide full reimbursement for these services.

7.32. Murphy, J.V., Patil, A. "Stimulation of the nervous system for the management of seizures: current and future developments." *CNS Drugs.* 2003;17(2):101-15. Publication Types: Review, Review, Tutorial.

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Vagal nerve stimulation (VNS) for the treatment of refractory epilepsy appears to have started from the theory that since VNS can alter the EEG, it may influence epilepsy. It proved effective in several models of epilepsy and was then tried in short-term, open-label and double-blind trials, leading to approval in Canada, Europe and the US. Follow-up observations in these patients demonstrated continued improvement in seizure control for up to 2 years. Close to 50% of treated patients have achieved at least a 50% reduction in seizure frequency. This therapy was also useful as rescue therapy for ongoing seizures in some patients; many patients are more alert. The initial trials were completed in patients >=12 years of age with refractory partial seizures. Subsequently, similar benefits were shown in patients with tuberous sclerosis complex, Lennox-Gastaut syndrome, hypothalamic hamartomas and primary generalised seizures. Implanting the generator and leads is technically easy, and complications are few. The method of action is largely unknown, although VNS appears to alter metabolic activity in specific brain nuclei. Considering that improvement in mood is frequently found in patients using VNS, it has undergone trials in patients with depression. Other illnesses deserving exploration with this unusual therapy are Alzheimer's disease and autism. Some aspects of VNS have proven disappointing. Although patients have fewer seizures, the number of antiepileptic drugs they take is not significantly reduced. In addition, there is no way to accurately predict the end of life of the generator. Optimal stimulation parameters, if they exist, are unknown. Deep brain stimulation is a new method for controlling medically refractory seizures. It is based on the observation that thalamic stimulation can influence the EEG over a wide area. Several thalamic nuclei have been the object of stimulation in different groups of patients. Intraoperative brain imaging is essential for electrode placement. The procedure is done under local anaesthesia. Experience with this therapy is currently limited, but growing.

7.33. Graham, A.J., Martin-Ruiz, C.M., Teaktong, T., Ray, M.A., Court, J.A. "Human brain nicotinic receptors, their distribution and participation in neuropsychiatric disorders." *Curr Drug Target CNS Neurol Disord.* 2002 Aug;1(4):387-97. Publication Types: Review, Review, Tutorial.

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Mapping of nicotinic acetylcholine receptor (nAChR) subtypes and subunits in human brain is far from complete, however it is clear that multiple subunits are present (including alpha3, alpha4, alpha5, alpha6 and alpha7, beta2, alpha3 and beta4) and that these receptors are not solely distributed on neurones, but also on cerebral vasculature and astrocytes. It is important to elucidate subunit composition of receptors associated with different cell types and pathways within the human CNS in terms of potential nicotinic therapy for a range of both developmental and age-related disorders in which nAChR attenuation occurs. Reductions in nAChRs are reported in Alzheimer's and Parkinson's diseases, dementia with Lewy

bodies, schizophrenia and autism, but may not be associated with reduced cortical cholinergic innervation observed in vascular dementia or occur at an early stage in Down's syndrome. Changes in nAChR expression in neuropsychiatric disorders appear to be brain region and subtype specific and have been shown in some instances to be associated with pathology and symptomatology. It is likely that deficits in alpha4-containing receptors predominate in cortical areas in Alzheimer's disease and autism, whereas reduction of alpha7 receptors may be more important in schizophrenia. Changes in astrocytic and vascular nAChR expression in neurodegenerative diseases should also be considered. Studies using both animal models and human autopsy tissue suggest that nAChRs can play a role in neuroprotection against age-related pathology. It is possible that the development of nAChR subtype specific drugs may lead to advances in therapy for both age-related and psychiatric disorders.

7.34. Gioia, G.A., Isquith, P.K., Kenworthy, L., Barton, R.M. "Profiles of everyday executive function in acquired and developmental disorders." *Neuropsychol Dev Cogn Sect C Child Neuropsychol.* 2002 Jun;8(2):121-37.

Children's National Medical Center, Washington, DC, USA.

Executive function profiles were examined within and between several clinical disorders via the multi-domain Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). Parent ratings of children with Inattentive and Combined types of Attention-Deficit/Hyperactivity Disorder (ADHD-I, ADHD-C), Autistic Spectrum Disorders (ASD), moderate and severe Traumatic Brain Injury (TBI), and Reading Disabilities (RD) were compared with controls. Profile analysis revealed significant ($p < .01$) and substantial ($\eta^2 > .10$) differences in global elevations and in profile of scale elevations between diagnostic groups. ASD, ADHD-I and ADHD-C groups exhibited greater elevations across the BRIEF scales than did RD and Severe TBI groups, who were in turn more elevated than Moderate TBI and Control groups. The ADHD-C group was unique in its frequency and severity of inhibitory deficits, while the ASD group was distinguishable by its deficits in flexibility. Within diagnostic groups, relative risk for executive dysfunction was calculated with variability present in the frequency of clinically elevated scales. While the BRIEF captures executive profiles characteristic of specific disorders in the clinical setting, it is not diagnostic in its own right and is best used within the context of a broad based evaluation.

7.35. Kandt, R.S. "Tuberous sclerosis complex and neurofibromatosis type 1: the two most common neurocutaneous diseases." *Neurol Clin.* 2002 Nov;20(4):941-64. Publication Types: Review, Review, Academic.

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TSC and NF1 are the most common of the neurocutaneous diseases, and both are autosomal dominant with a high spontaneous mutation rate. For diagnosis, two features are necessary for each disease. Skin findings for each are especially helpful for diagnosis, as is neuroimaging in TSC.

For NF1, neuroimaging is not yet reliable for diagnosis. In children, brain symptoms cause most of the morbidity in TSC, and nerve sheath and nervous system tumors as well as learning disabilities cause major morbidity in NF1. Renal disease becomes a serious problem for adults with TSC. The TSC1, TSC2, and NF1 genes function as tumor suppressor genes and have other functions that are being investigated. Blood tests for diagnosis have a high false-negative rate. Therapies for TSC and for NF1 are both medical and surgical.

7.36. Neuringer, A. "Operant variability: evidence, functions, and theory." *Psychon Bull Rev.* 2002 Dec;9(4):672-705. Publication Types: Review, Review, Tutorial.

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Although responses are sometimes easy to predict, at other times responding seems highly variable, unpredictable, or even random. The inability to predict is generally attributed to ignorance of controlling variables, but this article is a review of research showing that the highest levels of behavioral variability may result from identifiable reinforcers contingent on such variability. That is, variability is an operant. Discriminative stimuli and reinforcers control it, resulting in low or high variability, depending on the contingencies. Schedule-of-reinforcement effects are orderly, and choosing to vary or repeat is lawfully governed by relative reinforcement frequencies. The operant nature of variability has important implications. For example, learning, exploring, creating, and problem solving may partly depend on it. Abnormal levels of variability, including those found in psychopathologies such as autism, depression, and attention deficit hyperactivity disorder, may be modified through reinforcement. Operant variability may also help to explain some of the unique attributes of voluntary action.

7.37. Sivberg, B. "Coping strategies and parental attitudes, a comparison of parents with children with autistic spectrum disorders and parents with non-autistic children." *Int J Circumpolar Health.* 2002;61 Suppl 2:36-50.

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This study focused on the coping strategies of parents' with children with autistic spectrum disorders (ASD) and the relation between these strategies and parenting styles. Coping strategies were measured using the Sense of Coherence Scale (SOC) and the Purpose in Life Test (PIL-R). Parental attitudes toward loving care, stress, worry, and guilt feelings were assessed using the Family Impact Questionnaire. Two groups of participants were included: parents with children with ASD (EG) ($n = 66$) and a matched control group (CG) ($n = 66$). Paired Samples t-Test and Pearson's r correlation were used as methods of analysis. Main results distinguished significant ($p < .001$ to $.003$) differences between the EG and CG for almost all variables included. The M level of coping strategy was much higher for the CG than for the EG. SOC showed a stress-reducing effect in both the EG and CG. PIL-R explained 50% of the variance in SOC for the EG and 33% for the CG. The

only significant gender difference in the EG was on SOC indicating a higher sense of coherence among the fathers and probably an indicator of a stronger burnout effect of the mothers.

7.38. Bogte, H., Flamma, B., van der Meere, J. **"Do high functioning autistic individuals treated in a residential setting differ in divided attention abilities from those treated in an out-patient setting?"** *Int J Circumpolar Health*. 2002;61 Suppl 2:15-21.

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The goal of this current study was to test divided attention abilities of a group adults with autism and normal intellectual functioning, treated in a residential setting versus those treated in an out-patient setting. Both groups were compared with a control group using the Sternberg (1969) reaction time paradigm. It appeared that the in-patient group suffered from a divided attention deficit compared to a norm group. The patients treated in an out-patient setting scored in between the norm group and the in-patient group. Findings are discussed with respect to the relevance for the day to day clinical practice.

7.39. Findling, R.L. **"Use of quetiapine in children and adolescents."** *J Clin Psychiatry*. 2002;63 Suppl 13:27-31. Publication Types: Review, Review, Tutorial.

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The atypical antipsychotic quetiapine has been examined in children and adolescents in a randomized clinical trial, a number of open-label studies, and several chart review studies. Although only a small amount of information exists, most studies indicate that quetiapine is effective and well tolerated in various pediatric populations. Because quetiapine appears to be well tolerated in the young and associated with manifest salutary effects, it seems to be a promising agent that has potential for use in children and adolescents. This article reviews studies of quetiapine in the treatment of children and adolescents with a variety of psychiatric disorders. Despite these encouraging findings, the number of studies is small, and some have methodological limitations. Methodologically rigorous studies with substantive numbers of subjects are needed to confirm or refute these preliminary impressions.

7.40. Drew, A., Baird, G., Baron-Cohen, S., Cox, A., Slonims, V., Wheelwright, S., Swettenham, J., Berry, B., Charman, T. **"A pilot randomised control trial of a parent training intervention for pre-school children with autism. Preliminary findings and methodological challenges."** *Eur Child Adolesc Psychiatry*. 2002 Dec;11(6):266-72. Publication Types: Clinical Trial, Randomized Controlled Trial.

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Few attempts have been made to conduct randomised control trials (RCTs) of interventions for pre-school children with autism. We report findings of a pilot RCT for a parent training intervention with a focus on the development of joint attention skills and joint action routines. Twenty-four children meeting ICD-10 criteria for childhood autism (mean age = 23 months) were identified using the CHAT screen and randomised to the parent training group or to local services only. A follow-up was conducted 12 months later (mean age = 35 months). There was some evidence that the parent training group made more progress in language development than the local services group. However, the present pilot study was compromised by several factors: a reliance on parental report to measure language, non-matching of the groups on initial IQ, and a lack of systematic checking regarding the implementation of the parent training intervention. Furthermore, three parents in the local services group commenced intensive, home-based behavioural intervention during the course of the study. The difficulties encountered in the conduct of RCTs for pre-school children with autism are discussed. Methodological challenges and strategies for future well-designed RCTs for autism interventions are highlighted.

7.41. Sivberg, B. **"Family system and coping behaviors: a comparison between parents of children with autistic spectrum disorders and parents with non-autistic children."** *Autism*. 2002 Dec;6(4):397-409.

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The study deals with strain on the family system, as well as the level of coping and types of coping behavior of the parents, in families with a child diagnosed as having an autistic spectrum disorder (ASD) as compared to families in a control group. Thirty-seven families and 66 parents were involved in each case, and four psychological tests were used. It was found that lower levels of coping were associated with higher levels of strain on the family system, that the level of strain on the family system was greater in the families with a child with an ASD, and that the two groups differed in their pattern of coping behavior. It is argued that limited contact between the child with an ASD and its parents, claimed earlier to be a cause of autism, can be explained in terms of strain on the family system and the resulting pattern of coping.

7.42. Borchers, A.T., Keen, C.L., Shoenfeld, Y., Silva, J. Jr., Gershwin, M.E. **"Vaccines, viruses, and voodoo."** *J Investig Allergol Clin Immunol*. 2002;12(3):155-68. Publication Types: Review, Review, Tutorial.

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Vaccinations are invaluable in protection from a wide variety of diseases that can cause substantial morbidity and mortality. Although a rare complication of vaccination, autoimmune disorders represent one of these morbidities. Recently, widespread public concern has arisen from case reports suggesting that—similar to what has been observed after natural viral infections—there might be an association between specific immunizations and autoimmune diseases. Herein we

address the biological plausibility of such a connection, focusing particularly on the examples of hepatitis B, rubella, and measles-mumps-rubella (MMR) vaccinations, and the autoimmune diseases they are potentially associated with. Our review of the available data suggests that, for the general population, the risk: benefit ratio is overwhelmingly in favor of vaccinations. However, the possibility cannot be ruled out that, in genetically susceptible individuals, vaccination can result in the unmasking of an autoimmune disease triggered by the immunization. We also critically examine the existing data suggesting a link between immunization against MMR and autism, and briefly discuss the controversial evidence pointing to a possible relationship between mercury exposure from vaccines and autistic disorders. There is a continued urgent need for rigorously designed and executed studies addressing these potential associations, although the use of vaccinations remains a critical public health tool for protection against infectious disease.

7.43. Onda, H., Crino, P.B., Zhang, H., Murphey, R.D., Rastelli, L., Gould Rothberg, B.E., Kwiatkowski, D.J. "Tsc2 null murine neuroepithelial cells are a model for human tuber giant cells, and show activation of an mTOR pathway." *Mol Cell Neurosci.* 2002 Dec;21(4):561-74.

Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Cortical tubers are developmental brain malformations in the tuberous sclerosis complex (TSC) that cause epilepsy and autism in TSC patients whose pathogenesis is uncertain. Tsc2 null murine neuroepithelial progenitor (NEP) cells display persistent growth when growth factors are withdrawn, express GFAP at high levels, and have reduced expression of a set of early neuronal lineage markers. Tsc2 null NEP cells exhibit aberrant differentiation into giant cells that express both beta III-tubulin and GFAP and that are morphologically similar to giant cells in human tubers. Tsc2 null giant cells and tuber giant cells have similar transcriptional profiles. Tsc2 null NEP cells express high levels of phosphorylated S6kinase, S6, Stat3, and 4E-BP-1, which is reversed by treatment with rapamycin, an inhibitor of mTOR. We conclude that giant cells in human tubers likely result from a complete loss of TSC2 expression and activation of an mTOR pathway during cortical development.

7.44. Adolphs, R., Baron-Cohen, S., Tranel, D. "Impaired recognition of social emotions following amygdala damage." *J Cogn Neurosci.* 2002 Nov 15;14(8):1264-74.

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Lesion, functional imaging, and single-unit studies in human and nonhuman animals have demonstrated a role for the amygdala in processing stimuli with emotional and social significance. We investigated the recognition of a wide variety of facial expressions, including basic emotions (e.g., happiness, anger) and social emotions (e.g., guilt, admiration, flirtatiousness). Prior findings with a standardized set of stimuli indicated that recognition of social emotions can be

signaled by the eye region of the face and is disproportionately impaired in autism (Baron-Cohen, Wheelwright, & Jolliffe, 1997). To test the hypothesis that the recognition of social emotions depends on the amygdala, we administered the same stimuli to 30 subjects with unilateral amygdala damage (16 left, 14 right), 2 with bilateral amygdala damage, 47 brain-damaged controls, and 19 normal controls. Compared with controls, subjects with unilateral or bilateral amygdala damage were impaired when recognizing social emotions; moreover, they were more impaired in recognition of social emotions than in recognition of basic emotions, and, like previously described patients with autism, they were impaired also when asked to recognize social emotions from the eye region of the face alone. The findings suggest that the human amygdala is relatively specialized to process stimuli with complex social significance. The results also provide further support for the idea that some of the impairments in social cognition seen in patients with autism may result from dysfunction of the amygdala.

7.45. Kimmel, S.R. "Vaccine adverse events: separating myth from reality." *Am Fam Physician.* 2002 Dec 1;66(11):2113-20. Publication Types: Review, Review, Tutorial.

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Vaccines have turned many childhood diseases into distant memories in industrialized countries. However, questions have been raised about the safety of some vaccines because of rare but serious adverse effects that have been attributed to them. Pain, swelling, and redness at the injection site are common local reactions to vaccines. Fever and irritability may occur after some immunizations. Currently, no substantial evidence links measles-mumps-rubella vaccine to autism, or hepatitis B vaccine to multiple sclerosis. Thimerosal is being eliminated from routine childhood vaccines because of concerns that multiple immunizations with vaccines containing this preservative could exceed recommended mercury exposures. Family physicians should be knowledgeable about vaccines so that they can inform their patients of the benefits of immunization and any proven risks. If immunization rates fall, the incidence of vaccine-preventable illnesses may rise.

7.46. Steyaert, J., Fryns, J.P. "Psychiatric genetics: the case of single gene disorders." *Eur Child Adolesc Psychiatry.* 2002 Oct;11(5):201-9. Publication Types: Review, Review, Academic.

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Quantitative and molecular genetics have made important developments in the last three decades. There is increasing evidence of the role of heredity in the field of neuropsychiatric disorders in children. So far, only a few pathways between genes and behaviour have been unravelled. Quantitative genetics puts polygenic inheritance models forward. Molecular genetic research based on these models seems promising, but until now has provided only a limited explanation for the variance in the studied neuropsychiatric

disorders. In these models the complexity of the expression of a single gene grows exponentially with the number of genes involved. Consequently, research on the gene-phenotype relationships and phenotypical variability in such models is extremely complex. The candidate gene approach, in which the gene-phenotype pathway of a single gene is studied, is more manageable, and in our opinion essential in understanding multiple gene models. We discuss recent findings in the field and their relevance for neuropsychiatric phenotypes. Single gene defects will only explain a part of the range of neuropsychiatric disorders in children, but the evidence that this approach can generate may help to clarify neuropsychiatric phenotypes. The discovery of single gene disorders in subgroups of subjects with a neuropsychiatric phenotype may result in new perspectives for their treatment.

7.47. Arrieta, I., Nunez, T., Martinez, B., Perez, A., Telcz, M., Criado, B., Gainza, I., Lostao, C.M. "Chromosomal fragility in a behavioral disorder." *Behav Genet.* 2002 Nov;32(6):397-412.

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Numerous studies have shown there is consistent evidence implicating genetic factors in the etiology of autism. In some cases chromosomal abnormalities have been identified. One type of these abnormalities is gaps and breaks nonrandomly located in chromosomes, denominated fragile sites (FS). We cytogenetically analyzed a group of autistic individuals and a normal population, and we examined the FS found in both samples with the aim of (1) comparing their FS expression, (2) ascertaining whether any FS could be associated with our autistic sample, and (3) examining if there are differences between individual and pooled-data analyses. Different statistical methods were used to analyse the FS of pooled and individual data. Our results show that there are statistically significant differences in the spontaneous expression of breakages between patients and controls, with a minimal sex difference. Using the method for pooled data, eight autosomal FS have preferential expression in patients and five patients were found to be positive at FS Xq27.3. With the method per-individual analysis, four FS emerged as specific in our autistic sample. Inferences of FS from pooled data were different from those of individual data. The findings suggest that although analysis of pooled data is necessitated by the problem of sparse data, analysis of single individuals is essential to know the significance of FS in autism.

7.48. Astrinidis, A., Cash, T.P., Hunter, D.S., Walker, C.L., Chernoff, J., Henske, E.P. "Tuberin, the tuberous sclerosis complex 2 tumor suppressor gene product, regulates Rho activation, cell adhesion and migration." *Oncogene.* 2002 Dec 5;21(55):8470-6.

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Tuberous sclerosis complex (TSC) is a tumor suppressor gene syndrome characterized by seizures, mental retardation,

autism, and tumors of the brain, kidney, heart, retina, and skin. TSC is caused by mutations in either TSC1 or TSC2, both of which are tumor suppressor genes. Hamartin, the protein product of TSC1, was found to interact with the ezrin-radixin-moesin family of cytoskeletal proteins and to activate the small GTPase Rho. To determine whether tuberin, the TSC2 product, can also activate Rho, we stably expressed full-length human tuberin in two cell types: MDCK cells and ELT3 cells. ELT3 cells lack endogenous tuberin expression. We found that expression of human tuberin in both MDCK and ELT3 cells was associated with an increase in the amount of Rho-GTP, but not in Rac1-GTP or cdc42-GTP. Tuberin expression increased cell adhesion in both cell types, and decreased chemotactic cell migration in ELT3 cells. In MDCK cells, there was a decrease in the amount of total Focal Adhesion Kinase (FAK) and an increase in the fraction of phosphorylated FAK. These findings demonstrate for the first time that tuberin activates Rho and regulates cell adhesion and migration. Pathways involving Rho activation may have relevance to the clinical manifestations of TSC, including pulmonary lymphangioleiomyomatosis.

7.49. Olsson, M.B., Hwang, C.P. "Sense of coherence in parents of children with different developmental disabilities." *J Intellect Disabil Res* 2002 Oct;46(Pt 7):548-59.

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BACKGROUND: The aim of the present study was to test if Antonovsky's theory of sense of coherence can facilitate understanding: (1). individual differences in psychological adaptation in parents of children with intellectual disability (ID); and (2). why parents of children with ID generally experience higher levels of stress and depression than parents of children who develop normally. **METHODS:** Sense of coherence (SoC) and depression were assessed using the short SoC scale (13 items) and the Beck Depression Inventory in 216 families of children with ID and/or autism, and in 213 control families. **RESULTS:** It is argued that: (1). parents of children with ID with low SoC are at increased risk for developing depression compared to control parents with low SoC not experiencing this stressor; and (2). the life situation of parenting a child with ID may have a negative impact on parents' SoC levels that, in turn, will make them more vulnerable to experiencing stress and depression. **CONCLUSION:** The SoC theory is valuable in understanding individual differences in psychological adaptation in parents of children with ID.

7.50. Cullen, L., Barlow, J. "'Kiss, cuddle, squeeze': the experiences and meaning of touch among parents of children with autism attending a Touch Therapy Programme." *J Child Health Care* 2002 Sep;6(3):171-81. Publication Types: Clinical Trial.

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The aim of this qualitative study was to explore the experiences and meaning of touch between parents and

children with autism before and after attending a Touch Therapy Programme. The sample comprised 12 parents (1 father and 11 mothers) of children (1 female and 11 male) with autism. Parents were interviewed before and immediately after the 8-week programme. Pre-programme results suggested that children were controlling the experience of touch. Parents felt 'hurt' in response to the 'aloof nature of autism, and natural parenting instincts (e.g. spontaneous cuddles) were restricted. Post-programme results suggested that children appeared to tolerate touch. Parents reported that routine tasks (e.g. dressing) were accomplished more easily and that children appeared generally more relaxed. Parents reported feeling 'closer' to their children and felt that the touch therapy had opened a communication channel between themselves and their children.

7.51. Sandman, C.A., Touchette, P., Marion, S., Lenjavi, M., Chicz-Demet, A. "Disregulation of proopiomelanocortin and contagious maladaptive behavior." *Regul Pept* 2002 Oct 15;108(2-3):179-85. Publication Types: Multicenter Study.

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Self-injurious behavior (SIB) is an untreatable and often life-threatening problem among individuals with developmental disorders, especially those diagnosed with autism. Functioning, relationships and processing of the proopiomelanocortin (POMC) system are "uncoupled" in subgroups of self-injuring individuals resulting in different ratios of ACTH and opioids in the bloodstream, particularly under conditions of stress. In this study, relations between SIB and POMC were evaluated in a multi-year study of the largest prospective sample studied to date. Observations were collected on palmtop computers for 45 treatment-resistant patients who exhibited chronic SIB. Behavior of each subject was observed in natural settings without disruption or intrusion, for continuous, 2.5-h periods, two times a day (morning and afternoon), 4 days a week for two consecutive weeks, for a total of 40 h/subject. Blood was collected in the morning, late afternoon and immediately after an SIB episode on two separate occasions separated by at least 6 months. Levels of beta-endorphin (beta E) and ACTH were assayed by RIA. We discovered that the SIB was the best predictor of subsequent SIB. Moreover, the majority of subjects exhibited this contagious pattern of SIB. Levels of POMC fragments were reliable over a 6- to 9-month period. Subjects exhibiting POMC dysregulation characterized by high morning levels of beta E had the highest transitional probabilities of SIB (i.e. contagious patterns; $F=8.17$, $P<0.01$). These findings suggest that subjects with "contagious" SIB may represent a behavioral phenotype associated with dysregulated expression of the POMC gene.

7.52. Roane, H.S., Piazza, C.C., Cercone, J.J., Grados, M. "Assessment and treatment of vocal tics associated with Tourette's syndrome." *Behav Modif* 2002 Sep;26(4):482-98.

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A functional analysis suggested that a young man's vocal tics were maintained by automatic reinforcement. A preference assessment was conducted to identify stimuli that effectively competed with the occurrence of vocal tics. When used as components of a reinforcement-based intervention, however, these stimuli were ineffective at reducing the occurrence of vocal tics. Observations conducted in a naturalistic context led to the hypothesis that variations in tics were associated with body positioning. Thus, an additional analysis was conducted to determine if vocal tics occurred less when the participant was lying down versus when he was seated upright. Results suggested that a combination of procedures might be useful in developing idiosyncratic interventions for automatically reinforced problem behavior, such as vocal tics.

7.53. Yazbak, F.E., Diodati, C.J. "Postpartum live virus vaccination: lessons from veterinary medicine." *Med Hypotheses* 2002 Sep;59(3):280-2. Publication Types: Review, Review, Tutorial.

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Pregnant rubella-susceptible women are often revaccinated during the postpartum period with the Measles, Mumps, and Rubella vaccine (MMR). It is known that the rubella virus from vaccine is secreted in breast milk and persists in the nose and throat for up to 28 days but it is not known whether the measles and mumps viruses are similarly secreted. It is probable the measles virus from vaccine is.

7.54. Geiger, D.M., Smith, D.T., Creaghead, N.A. "Parent and professional agreement on cognitive level of children with autism." *J Autism Dev Disord* 2002 Aug;32(4):307-12.

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The aim of the study was to compare the extent of agreement between parents and professional evaluators regarding the cognitive level of children with autism. We sought to determine the degree of parent and standardized test agreement about the child's cognitive level for children at different levels of cognitive functioning. Information regarding parental view of cognitive levels was collected from the questionnaires used during the initial evaluation. These levels were compared with age equivalencies obtained by professionals from standardized intellectual measures. Significant difference between parental perception and professional assessment of the child's cognitive level was found. In addition, there was significant correlation between the level of agreement and cognitive functioning; agreement increased as the level of cognitive functioning increased.

7.55. Danysz, W. "CX-516 Cortex pharmaceuticals." *Curr Opin Investig Drugs* 2002 Jul;3(7):1081-8. Publication Types: Review, Review, Tutorial.

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CX-516 is one of a series of AMPA modulators under development by Cortex, in collaboration with Shire and Servier, for the potential treatment of Alzheimer's disease (AD), schizophrenia and mild cognitive impairment (MCI) [234221]. By June 2001, CX-516 was in phase II trials for both schizophrenia and attention deficit hyperactivity disorder (ADHD) [412513]. A phase II trial in fragile X syndrome and autism was expected to start in May 2002 [449861]. In October 2001, Cortex was awarded a Phase II SBIR grant of \$769,818 from the National Institutes of Mental Health to investigate the therapeutic potential of AMPAkinines in schizophrenia. This award was to support a phase IIb study of CX-516 as a combination therapy in schizophrenia patients concomitantly treated with olanzapine. The trial was to enroll 80 patients and employ a randomized, double-blind, placebo-controlled design in which the placebo group was to receive olanzapine plus placebo and the active group was to receive olanzapine plus CX-516 [425982]. In April 2000, Shire and Cortex signed an option agreement in which Shire was to evaluate CX-516 for the treatment of ADHD. Under the terms of the agreement, Shire would undertake a double-blind, placebo-controlled evaluation of CX-516 involving ADHD patients. If the study proved effective, Shire would have the right to convert its option into an exclusive worldwide license for the AMPAkinines for ADHD under a development and licensing agreement. Should Shire elect to execute this agreement, Shire would bear all future developmental costs [363618]. By February 2002, Cortex and Servier had revealed their intention to begin enrolment for an international study of an AMPAkinine compound as a potential treatment for MCI in the near future. Assuming enrollment proceeded as anticipated, results were expected during the second quarter of 2003 [439301]. By May 2002, phase II trials were underway [450134]. In March 2002, Cortex was awarded extended funding under the University of California BioSTAR project for the research project: 'Ampakine modulation of brain neurotrophin expression: a novel therapeutic strategy'. This funding was expected to amount to \$193,000 over a two-year period [444872].

7.56. Crnic, L.S. "The Colorado mental retardation and developmental disabilities research center." *Int J Dev Neurosci* 2002 Jun-Aug;20(3-5):297-9. Publication Types: Review, Review, Tutorial.

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The Colorado MRRC was one of the original MRRCs funded and has maintained its focus on genetic and nutritional causes of mental retardation and developmental disabilities. Significant discoveries of the center have included a number of metabolic disorders, including glutaric academia types I and II, electron transport flavoprotein (ETF) deficiency, ETF dehydrogenase deficiency, glycerol kinase deficiency, sphingolipidoses, genetic linkages in dyslexia, phonological deficits in dyslexia, and the importance of the trace mineral Zn in early development. Current research at the center is supported by program of projects grants on inborn errors of metabolism, Down syndrome (DS), autism, and dyslexia.

7.57. Casanova, M.F., Buxhoeveden, D.P., Cohen, M., Switajala, A.E., Roy, E.L. "Minicolumnar pathology in dyslexia." *Ann Neurol* 2002 Jul;52(1):108-10.

Department of Psychiatry and Neurology, Medical College of Georgia, Augusta, USA.

The minicolumn is an anatomical and functional unit of the brain whose genesis accrues from germinal cell divisions in the ventricular zone of the brain. Disturbances in the morphometry of minicolumns have been demonstrated recently for both autism and Down's syndrome. We report minicolumnar abnormalities in the brain of a dyslexic patient. The corresponding developmental disturbance (ie, large minicolumns) could account for the perceptual errors observed in dyslexia.

7.58. Noterdaeme, M., Mildenerger, K., Sitter, S., Amorosa, H. "Parent information and direct observation in the diagnosis of pervasive and specific developmental disorders." *Autism* 2002 Jun;6(2):159-68.

Heckscher Klinik für Kinder- und Jugendpsychiatrie, Abteilung für teillesistung- und verhaltensgestörte Kinder, München, Germany.

Children with autism and children with a severe specific receptive language disorder show clear deficits in communicative language skills and social relationships. In this study the usefulness of a standardized parent interview (ADI-R) and a standardized observation schedule (ADOS-G) for the differential diagnosis of these two groups was assessed. Eleven children with early infantile autism and 16 children with a specific receptive language disorder participated. The parent interview was conducted with all parents and the observation schedule was administered to all children. Ten out of 11 children with autism were correctly classified as having autism on the ADI-R and the ADOS-G. One child with a receptive language disorder was falsely classified as having autism on the ADI-R, and none on the ADOS-G. Parent interview provides extensive information on the developmental course of the child. Direct observation gives an overview of actual relevant behavioural problems. The two instruments are complementary in the diagnosis of developmental disorders.

7.59. Bibby, P., Eikeseth, S., Martin, N.T., Mudford, O.C., Reeves, D. "Progress and outcomes for children with autism receiving parent-managed intensive interventions." *Res Dev Disabil* 2002 Jan-Feb;23(1):81-104. Publication Types: Published Erratum.

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Parent-managed behavioral interventions for young children with autism are under-researched. We analysed data from 66 children served by 25 different early intervention consultants. After a mean of 31.6 months of intervention, IQ scores had not changed (N = 22). Vineland adaptive behavior scores had increased significantly by 8.9 points (N = 21). No children aged >72 months attained normal functioning, i.e., IQ > 85

and unassisted mainstream school placement (N = 42). Progress for 60 children across 12 months was found for mental age (5.4 months), adaptive behavior (9.7 months), and language (5.1 months). The interventions did not reproduce results from clinic-based professionally directed programs. The effectiveness of the parent-managed intervention model as it has developed and the adequacy of professional services in that model are discussed.

7.60. Luckett, T., Powell, S.D., Messer, D.J., Thornton, M.E., Schulz, J. "Do children with autism who pass false belief tasks understand the mind as active interpreter?" *J Autism Dev Disord* 2002 Apr;32(2):127-40.

Department of Education, University of Hertfordshire, Watford, United Kingdom.

Interpretive diversity is the term used by Carpendale and Chandler (1996) to refer to the fact that two individuals exposed to precisely the same stimulus may interpret it in quite different, but equally plausible, ways. An appreciation of interpretive diversity is said by Carpendale and Chandler to represent a development in understanding that is qualitatively different from that necessary to succeed on false belief tasks. A study is reported in which children with autism and children with general delay were given a battery of tasks consisting of false belief tasks and tasks designed to test for an understanding of interpretive diversity. Findings from the present study offer limited support for Carpendale and Chandler's claim that tasks which test for an understanding of interpretive diversity may be more difficult than false belief tasks. Between-group differences in the consistency and quality of responses given by participants suggest that autistic and delayed children may have differed somewhat in their approach to the tasks given.

7.61. Baker, H.C. "A comparison study of autism spectrum disorder referrals 1997 and 1989." *J Autism Dev Disord* 2002 Apr;32(2):121-5.

Child and Adolescent Mental Health Service, Belconnen, ACT, Australia.

A number of overseas studies have indicated an increase in the prevalence of Autism Spectrum Disorder (ASD). In the Australian Capital Territory, information (number, age, sex, final diagnosis) was gathered on all children referred for suspected ASD to Child and Adolescent Mental Health Service during 1997, and the findings were compared with those from a similar study in 1989. It was found that (1) there was a 200% increase in positive diagnoses of ASD in 1997 despite a 0.5% decrease in population, (2) there was a wider age range in the 1997 cohort, (3) there was a 26% increase in milder cases in 1997, and (4) the ratio of boys to girls decreased from 8:1 in 1989 to 3.5:1 in 1997. These findings are compared with those overseas, and questions are raised for further exploration.

7.62. Reddy, V., Williams, E., Vaughan, A. "Sharing humour and laughter in autism and Down's syndrome." *Br J Psychol* 2002 May;93(Pt 2):219-42.

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Everyday humour and laughter can tell us about children's ability to engage with and understand others. A group of 19 pre-school children with autism and 16 pre-school children with Down's syndrome, matched on non-verbal mental age, participated in a cross-sectional study. Parental reports revealed no group differences in overall frequencies of laughter or laughter at tickling, peekaboo or slapstick. However, in the autism group, reported laughter was rare in response to events such as funny faces or socially inappropriate acts, but was common in strange or inexplicable situations. Reported responses to others' laughter also differed: children with autism rarely attempted to join in others' laughter and rarely attempted to re-elic it through acts of clowning or teasing. Analysis of videotaped interactions also showed no group differences in frequencies of child or adult laughter. However, the children with autism showed higher frequencies of unshared laughter in interactive situations and lower frequencies of attention or smiles in response to others' laughter. Humour is an affective and cultural phenomenon involving the sharing of affect, attention and convention; children with autism show problems in some simple affective and mutual as well as joint attentional and cultural aspects of humorous engagement.

7.63. Dykens, E.M. "Are jigsaw puzzle skills 'spared' in persons with Prader-Willi syndrome?" *J Child Psychol Psychiatry* 2002 Mar;43(3):343-52.

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BACKGROUND: This three-part study examines previous clinical impressions that people with Prader-Willi syndrome have unusual jigsaw puzzle and word search skills. **RESULTS:** Children with Prader-Willi syndrome showed relative strengths on standardized visual-spatial tasks (Object Assembly, Triangles, VMI) in that their scores were significantly higher than age- and IQ-matched peers with mixed mental retardation, but below those of age-matched normal children with average IQs. In striking contrast, children with Prader-Willi syndrome scored on par with normal peers on word searches, and they far outperformed them on the jigsaw puzzles, placing more than twice as many pieces as the typically-developing group. Within Prader-Willi syndrome, puzzle proficiency was not predicted by age, IQ, gender, degree of obesity, or obsessive-compulsive symptoms, but by genetic subtypes of this disorder. **CONCLUSIONS:** Findings are discussed in relation to splinter skills in autism, and to cases with autism and chromosome 15 anomalies that include the Prader-Willi region.

7.64. Leekam, S.R., Libby, S.J., Wing, L., Gould, J., Taylor, C. "The Diagnostic Interview for Social and Communication Disorders: algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder." *J Child Psychol Psychiatry* 2002 Mar;43(3):327-42. Publication Types: Evaluation Studies.

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BACKGROUND: The Diagnostic Interview for Social and Communication Disorders (DISCO) is an interviewer-based schedule for use with parents and carers. In addition to its primary clinical purpose of helping the clinician to obtain a developmental history and description of the child or adult concerned, it can also be used to assist in providing a formal diagnostic category. **METHOD:** In this study we compared two algorithms based on the ninth revision of the schedule (DISCO 9). The algorithm for ICD-10 childhood autism comprised 91 individual, operationally defined items covering the behaviour outlined in the ICD-10 research criteria. The algorithm for the autistic spectrum disorder, as defined by Wing and Gould (1979), was based on 5 DISCO items that represented overarching categories of behaviour crucial for the diagnosis of autistic disorders. The aim of the study was to examine the implications for clinical diagnosis of these two different approaches. Parents of 36 children with clinical diagnoses of autistic disorder, 17 children with learning disability and 14 children with language disorders were interviewed by two interviewers. Algorithm diagnoses were applied to interview items in order to analyse the relationship between clinical and algorithm diagnoses and the inter-rater reliability between interviewers. **RESULTS:** Clinical diagnosis was significantly related to the diagnostic outputs for both algorithms. Inter-rater reliability was also high for both algorithms. The ICD childhood disorder algorithm produced more discrepant diagnoses than the Wing and Gould autistic spectrum algorithm. Analysis of the ICD-10 algorithm items and combination of items helped to explain the reason for these discrepancies. **CONCLUSIONS:** The results indicate that the DISCO is a reliable instrument for diagnosis when sources of information are used from the whole interview. It is particularly effective for diagnosing disorders of the broader autistic spectrum.

7.65. Wing, L., Leekam, S.R., Libby, S.J., Gould, J., Locombe, M. "The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use." *J Child Psychol Psychiatry* 2002 Mar;43(3):307-25. Publication Types: Evaluation Studies.

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BACKGROUND: The Diagnostic Interview for Social and Communication Disorders (DISCO) is a schedule for the diagnosis of autistic spectrum and related disorders and assessment of individual needs. It enables information to be recorded systematically for a wide range of behaviours and developmental skills and is suitable for use with all ages and levels of ability. In addition to helping the clinician to obtain a profile of each individual's pattern of development and behaviour, the DISCO also enables identification of specific features found in autistic spectrum disorders that are relevant for use with established diagnostic systems. **METHOD:** This paper describes the historical background of the DISCO, outlines its structure and reports the results of an inter-rater

reliability study with parents of 82 children aged 3 to 11 years with autistic spectrum disorder, learning disability, language disorder or typical development. **RESULTS:** Inter-rater reliability for the items in the interview was high (kappa coefficient or intra-class correlation at .75 or higher). This level of agreement was achieved for over 80% of the interview items.

7.66. Celani, G. "Human beings, animals and inanimate objects: what do people with autism like?" *Autism* 2002 Mar;6(1):93-102.

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An experimental strategy based on the 'sorting by preference' approach was used to obtain information about the nature of the autistic syndrome. Twelve participants with autism (mean age 11:9 years), 12 with Down's syndrome (mean age 11:5 years) and 12 typically developing children (mean age 6:2 years) were matched on gender (M:F 9:3) and on verbal mental age. In a forced choice procedure they had to choose between: human beings or inanimate objects (relatedness condition); animals or inanimate objects (animate condition); drawings of a child handling a thing or of the same child in contact with another person (interpersonal relationship condition); pleasant or unpleasant situations without living beings (control condition). The performances of the groups differed only on the relatedness condition and on the interpersonal relationship condition. The results are discussed in the context of the social difficulties experienced by individuals with autism.

7.67. Weiss, M.J. "Hardiness and social support as predictors of stress in mothers of typical children, children with autism, and children with mental retardation." *Autism* 2002 Mar;6(1):115-30.

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This study assessed the effects of social support and hardiness on the level of stress in mothers of typical children and children with developmental disabilities. One hundred and twenty mothers participated (40 mothers of children with autism, 40 mothers of children with mental retardation, and 40 mothers of typically developing children). Results indicated significant group differences in ratings of depression, anxiety, somatic complaints and burnout. Regression analyses were conducted to determine the best predictors of the dependent measures. Both hardiness and social support were predictive of successful adaptation. The relationships among hardiness, support and coping are discussed.

7.68. Tunali, B., Power, T.G. "Coping by redefinition: cognitive appraisals in mothers of children with autism and children without autism." *J Autism Dev Disord* 2002 Feb;32(1):25-34.

University of Houston, Texas, USA.

To test a model of how mothers cope with the stresses of raising a child with autism (Tunali & Power, 1993), mothers

of children with and without autism were interviewed. As predicted, mothers of autistic children: (1) placed less emphasis on career success and were more likely to believe that mothers of young children should not work outside of the home; (2) spent more leisure time with their extended family; (3) placed less emphasis on others' opinions of their child's behavior; (4) placed more emphasis on spousal support and parental roles in their discussions of marriage; (5) had more difficulty understanding their child's behavior; and (6) showed a marginally significant difference in their tolerance of ambiguity. Moreover, mothers of children with autism who showed these characteristics had the greatest life satisfaction overall.

7.69. McIntyre, L.L., Blacher, J., Baker, B.L. "Behaviour/mental health problems in young adults with intellectual disability: the impact on families." *J Intellect Disabil Res* 2002 Mar;46(Pt 3):239-49.

University of California, Riverside, California, USA.

BACKGROUND: The present authors studied the impact of dual diagnosis [i.e. intellectual disability (ID) and mental disorder] in young adults on their mothers' perceived levels of stress and decisions about placement. **METHODS:** The mothers of 103 young adults with severe ID were interviewed using a 2-3-h in-depth protocol of measures designed to assess their child's adaptive functioning, maladaptive behaviour, mental health problems and negative impact on the family, as well as their own thoughts on out-of-home placement. The Scales of Independent Behavior—Revised Problem Behavior Scale assessed problem behaviours and the Reiss Screen assessed mental disorder. **RESULTS:** These measures were highly correlated ($r = 0.64$), but tapped some different domains of maladaptive behaviour and proved to be most predictive when employed together. Behaviour and/or mental health (B/MH) problems significantly predicted the mothers' perceived negative impact of the young adult on the family, even after controlling for other young adult characteristics. These problems also predicted the family's steps toward seeking out-of-home placement, as did better young adult health and the mother's higher educational attainment; stress did not predict additional variance in placement once these variables were accounted for. **CONCLUSIONS:** The discussion focuses on the implications for service provision to families of young adults with B/MH problems.

7.70. Hellzen, O., Asplund, K. "Being in a fragmented and isolated world: interviews with carers working with a person with a severe autistic disorder." *J Adv Nurs* 2002 Feb;37(4):346-54.

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AIM: To illuminate the meaning of being a carer for a person with a severe autistic disorder. **BACKGROUND:** Carers working with people with severe autism are occasionally exposed to residents' self-injurious behaviours and violent actions and at times residents appear resistant to all forms of treatment. **DESIGN/METHOD:** A qualitative case study was

conducted. Six Swedish carers/enrolled nurses (ENs), working on a special ward in a nursing home were interviewed about their lived experiences when caring for an individual with a severe autistic disorder. Narrative interviews were conducted and interpreted using a phenomenological-hermeneutic method inspired by Paul Ricoeur. **FINDINGS:** Two themes were formulated which describe the carers' reality and their dream of an ideal. This ideal described carers' experiences of being trapped in a segmented and isolated care reality and their longing to achieve a sense of wholeness. The findings were interpreted and reflected on in the light of a framework inspired by the German philosopher Karl Jaspers in order to achieve a deeper understanding of the text. **CONCLUSIONS:** In their desperation, the carers used their empirical knowledge based on scientific knowledge, which could be understood as a substitute for their vision of a consoling wholeness. This paper shows that searching for a substitute to consolation seems to be an important aspect of the meaning of being a carer for a person with a severe autistic disorder.

7.71. Sergeant, J.A., Geurts, H., Oosterlaan, J. "How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder?" *Behav Brain Res* 2002 Mar 10;130(1-2):3-28. Publication Types: Review, Review, Academic.

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A selective review of research in the executive functioning (EF) is given for attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), higher functioning autism (HFA) and Tourette syndrome. The review is restricted due to changes in the classification of the disorder in recent years and secondly the heterogeneity of EF is restricted to five key areas of concern, inhibition, set shifting, working memory, planning, and fluency. The review makes clear that there are strong differences between child psychopathological groups and controls on these EFs. However, future research will be needed to identify an EF deficit or profile, which is specific for these disorders.

7.72. Grimaldi, B.L. "The central role of magnesium deficiency in Tourette's syndrome: causal relationships between magnesium deficiency, altered biochemical pathways and symptoms relating to Tourette's syndrome and several reported comorbid conditions." *Med Hypotheses* 2002 Jan;58(1):47-60.

BonnieGr@aol.com

Prior studies have suggested a common etiology involved in Tourette's syndrome and several comorbid conditions and symptomatology. Reportedly, current medications used in Tourette's syndrome have intolerable side-effects or are ineffective for many patients. After thoroughly researching the literature, I hypothesize that magnesium deficiency may be the central precipitating event and common pathway for the subsequent biochemical effects on substance P, kynurenine, NMDA receptors, and vitamin B6 that may result in the

symptomatology of Tourette's syndrome and several reported comorbid conditions. These comorbid conditions and symptomatology include allergy, asthma, autism, attention deficit hyperactivity disorder, obsessive compulsive disorder, coprolalia, copropraxia, anxiety, depression, restless leg syndrome, migraine, self-injurious behavior, autoimmunity, rage, bruxism, seizure, heart arrhythmia, heightened sensitivity to sensory stimuli, and an exaggerated startle response. Common possible environmental and genetic factors are discussed, as well as biochemical mechanisms. Clinical studies to determine the medical efficacy for a comprehensive magnesium treatment option for Tourette's syndrome need to be conducted to make this relatively safe, low side-effect treatment option available to doctors and their patients. Copyright 2002 Harcourt Publishers Ltd.

7.73. Pletnikov, M.V., Moran, T.H., Carbone, K.M. "Borna disease virus infection of the neonatal rat: developmental brain injury model of autism spectrum disorders." *Front Biosci* 2002 Mar 1;7:d593-607. Publication Types: Review, Review, Tutorial.

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Autism spectrum disorders (ASD) have been the focus of a great deal of research and clinical speculation. This intense interest relates to both the perplexing pathogenesis and devastating consequences of these disorders. One of the obstacles to understanding the pathogenesis of autism and its efficient treatment has been the paucity of animal models that could be used for hypotheses-driven mechanistic studies of abnormal brain and behavior development and for the pre-clinical testing novel pharmacological treatments. The present review provides a detailed analysis of a new animal model of ASD. This model utilizes neonatal Borna disease virus (BDV) infection of the rat brain as a unique experimental teratogen to study the pathogenesis of neurodevelopmental damage. For more than a decade, studies of the BDV animal model have yielded much insight into the pathogenic processes of abnormal brain development and resulting autistic-like behavioral abnormalities in rats. The most recent experiments demonstrate the utility of the BDV model for studying the pathophysiological mechanisms of the gene-environment interaction that determines differential disease outcomes and variability in responses to treatments.

7.74. Patterson, P.H. "Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness." *Curr Opin Neurobiol* 2002 Feb;12(1):115-8.

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Direct viral infection of the developing brain can have disastrous consequences for the fetus. More subtle and perhaps more insidious are viral infections of the pregnant mother, which can have long-lasting effects such as an increased risk of schizophrenia in the offspring. A recent mouse model has shown that respiratory infection in the

pregnant mother leads to marked behavioral and pharmacological abnormalities in the offspring, some of which are relevant for schizophrenia and autism. This effect on fetal brain development might be caused by the maternal antiviral immune response, possibly mediated by cytokines.

7.75. Bartolo, P.A. "Communicating a diagnosis of developmental disability to parents: multiprofessional negotiation frameworks." *Child Care Health Dev* 2002 Jan;28(1):65-71.

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It is a hard task for professionals to give and parents to receive the bad news about a child's developmental disability. This study describes how findings about four preschool children, with difficulties suspected to lie within the autistic spectrum, were negotiated with parents by two multiprofessional groups, one in a Medical (Site M) and one in an Education setting (Site E). Each assessment was undertaken over half a day, the professionals jointly interacting with the child and family. All assessment discussions were audiotaped and each participant was interviewed after the assessment. Conversation analysis showed the activation of three major social-interaction frameworks: professionals at both sites applied a parent-friendly frame, but this was complemented by a hopeful-diagnostic-formulation frame at Site M, and a defocusing-of-bad-news frame at Site E.

7.76. Lerner, V., Miodownik, C., Kapsan, A., Cohen, H., Loewenthal, U., Kotler, M. "Vitamin B6 as add-on treatment in chronic schizophrenic and schizoaffective patients: a double-blind, placebo-controlled study." *J Clin Psychiatry* 2002 Jan;63(1):54-8. Publication Types: Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial .

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BACKGROUND: Vitamin B6, or pyridoxine, plays an intrinsic role in the synthesis of certain neurotransmitters that take part in development of psychotic states. Several reports indicate that vitamin B6 may be a factor in a number of psychiatric disorders and related conditions, such as autism, Alzheimer's disease, hyperactivity, learning disability, anxiety disorder, and depression. Moreover, there are anecdotal reports of a reduction in psychotic symptoms after vitamin B6 supplementation of psychopharmacologic treatment of patients suffering from schizophrenia or organic mental disorder. The aim of this study was to examine whether vitamin B6 therapy influences psychotic symptoms in patients suffering from schizophrenia and schizoaffective disorder. **METHOD:** The effects of the supplementation of vitamin B6 to antipsychotic treatment on positive and negative symptoms in 15 schizophrenic and schizoaffective patients (DSM-IV criteria) were examined in a double-blind, placebo-controlled, crossover study spanning 9 weeks. All patients had stable psychopathology for at least 1 month before entry into the study and were maintained on treatment with their prestudy

psychoactive and antiparkinsonian medications throughout the study. All patients were assessed using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia on a weekly basis. Patients randomly received placebo or vitamin B6, starting at 100 mg/day in the first week and increasing to 400 mg/day in the fourth week by 100-mg increments each week. RESULTS: PANSS scores revealed no differences between vitamin B6- and placebo-treated patients in amelioration of their mental state. CONCLUSION: Further studies with larger populations and shorter duration of illness are needed to clarify the question of the possible efficacy of vitamin B6 in treatment of psychotic symptoms in schizophrenia.

7.77. Licht, D.J., Lynch, D.R. "Juvenile dentatorubral-pallidoluysian atrophy: new clinical features." *Pediatr Neurol* 2002 Jan;26(1):51-4.

Division of Child Neurology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

Dentatorubral-pallidoluysian atrophy is a rare autosomal-dominant neurodegenerative disorder caused by an expansion of a CAG repeat in the atrophin-1 gene on chromosome 12. Dentatorubral-pallidoluysian atrophy is characterized clinically by prominent anticipation and a wide variety of symptoms that depend on age of onset and number of trinucleotide repeats. The juvenile type of dentatorubral-pallidoluysian atrophy, like Huntington's disease, is most commonly inherited via paternal transmission of the gene and most frequently presents with early-onset progressive myoclonus epilepsy with mental retardation and ataxia. We present six affected individuals with dentatorubral-pallidoluysian atrophy from a black family living in North America. This pedigree includes two severe juvenile-onset cases, one of maternal transmission and the other of paternal transmission. Both cases of juvenile-onset disease presented with autistic features and seizures. Interestingly, cranial magnetic resonance imaging performed on the more affected child revealed only mild cerebellar atrophy. The present family expands the clinical description of juvenile-onset dentatorubral-pallidoluysian atrophy and emphasizes the importance of considering dentatorubral-pallidoluysian atrophy in children with progressive myoclonus epilepsy.

7.78. Gandhi, S., Rubinstein, I., Tsueshita, T., Onyuksel, H. "Secretin self-assembles and interacts spontaneously with phospholipids in vitro." *Peptides* 2002 Jan;23(1):201-4.

Department of Bioengineering, University of Illinois at Chicago, 60612, USA.

Secretin, a 27-amino acid neuropeptide, is a member of the secretin/glucagon/vasoactive intestinal polypeptide (VIP) superfamily of amphipathic peptides. The peptide modulates gastrointestinal and neuronal function and is currently being evaluated for the treatment of autism. However, as most peptides, it has a short circulation half-life. Previously, we have shown that VIP self-assembles in aqueous environment and interacts with a biomimetic phospholipid membrane. These in vitro characteristics increase VIP half-life and

bioactivity in vivo. The purpose of this study was to investigate whether secretin exhibits similar properties in vitro by forming micelles in aqueous solution and interacting with phospholipids. Results of this study demonstrated that secretin self-assembles to form micelles in HEPES buffer at 25 degrees C above approximately 0.4 microM. Additionally, secretin interacts with a biomimetic phospholipid membrane as indicated from a significant increase in membrane surface pressure (from 25.5 +/- 1.3 to 32.5 +/- 3.0, P < 0.05). Importantly, the peptide undergoes conformational transition from predominantly random coil in saline to alpha-helix in the presence of phospholipid, distearoyl-phosphatidylcholine-poly(ethylene) glycol (mol mass 2000) micelles. We suggest that these distinct biophysical attributes could modulate secretin bioactivity in vivo.

7.79. Shook, G.L., Ala'i-Rosales, S., Glenn, S.S. "Training and certifying behavior analysts." *Behav Modif* 2002 Jan;26(1):27-48.

Department of Behaviour Analysis, University of North Texas, USA.

Proper professional certification and training of behaviour analysts who work with individuals with autism is critical in ensuring that those individuals receive the highest quality behavior analytic services. This article discusses the current issues surrounding certification of behavior analysts and describes the important features of the Behavior Analyst Certification Board and its credentials. The article also reviews approaches to the training content for behavior analysts who work with persons with autism. The interrelationship between training and certification is explored.

7.80. Aylott, J. "Understanding and listening to people with autism." *Br J Nurs* 2001 Feb 8-21;10(3):166-72. Publication Types: Review, Review, Tutorial.

Sheffield Hallam University.

This article continues the learning disability supplement's examination of autism (see Aylott, 2000a,b) by exploring how a lack of knowledge and understanding of positive aspects of autism among non-autistic people (neuro typicals) has led to many adults with autism having negative life experiences. It calls for all staff working with people with autism to find ways to 'think' and 'feel' in autism. It is only when this has been achieved that any of us will be able to listen effectively to people with autism; this hopefully may result in life experiences for people with autism being more of a positive than a negative encounter.

7.81. Kerrell, H. "Service evaluation of an autism diagnostic clinic for children." *Nurs Stand* 2001 Jun 6-12;15(38):33-7. Publication Types: Evaluation Studies

Autism Diagnostic Clinic, Gwent Healthcare NHS Trust, Gwent.

AIM: To examine parents' personal experiences of a diagnostic clinic for children suspected of having autistic spectrum disorder, and to evaluate parental satisfaction with the

multidisciplinary assessment team at the clinic. **METHOD:** A structured interview schedule was designed to obtain information from parents. The questionnaire consisted of set questions divided into four sections using closed and open-ended questions. Interviews were conducted in the parents' homes over a period of one hour. **RESULTS:** All families whose child had been diagnosed by the clinic were contacted and invited to take part in the study. Of a total of 24 families, parents from 11 families were interviewed. Responses indicated that although many parents were dissatisfied with the clinic, they would continue to attend appointments and recommend the clinic to others requiring this service. **CONCLUSION:** The findings of this small-scale study highlight the need for improved services for parents and families of children with autistic spectrum disorder attending the clinic. Better collaboration between members of the multidisciplinary team and parents is required to address the needs of this group of people.

7.82. Blackford, J.K. "Immunization controversy: understanding and addressing public misconceptions and concerns." *J Sch Nurs* 2001 Feb;17(1):32-7. Publication Types: Review, Review, Tutorial.

San Diego State University, CA, USA.

School nurses often meet with parents who are reluctant to immunize their children. This reluctance is based on widely publicized stories about vaccine safety. Illnesses that are preventable by vaccines have become almost nonexistent, and consequently, vaccine safety concerns have increased in prominence. Often a negative report about the risk of a particular vaccine is released by the media and on the Internet before scientific evidence has been obtained. To adequately respond to parental concerns, school nurses should be aware of the historical impact of vaccine safety issues and the vaccine-related fears that are prevalent at the present time. Nurses also need to be provided with scientifically accurate information so that risk-benefit concerns regarding vaccine safety can be effectively communicated to parents. In this way, school nurses can play an important role in ensuring that the student population and the community are protected from vaccine-preventable diseases.

7.83. Boyar, F.Z., Whitney, M.M., Lossie, A.C., Gray, B.A., Keller, K.L., Stalker, H.J., Zori, R.T., Geffken, G., Mutch, J., Edge, P.J., Voeller, K.S., Williams, C.A., Driscoll, D.J. "A family with a grand-maternally derived interstitial duplication of proximal 15q." *Clin Genet* 2001 Dec;60(6):421-30.

Raymond C. Philips Unit, Division of Pediatric Genetics, Department of Pediatrics and Center for Mammalian Genetics, University of Florida College of Medicine, Gainesville 32610-0296, USA.

About 1% of individuals with autism or types of pervasive developmental disorder have a duplication of the 15q11-q13 region. These abnormalities can be detected by routine G-banded chromosome study, showing an extra marker chromosome, or demonstrated by fluorescence in situ

hybridization (FISH) analysis, revealing an interstitial duplication. We report here the molecular, cytogenetic, clinical and neuropsychiatric evaluations of a family in whom 3 of 4 siblings inherited an interstitial duplication of 15q11-q13. This duplication was inherited from their mother who also had a maternally derived duplication. Affected family members had apraxia of speech, phonological awareness deficits, developmental language disorder, dyslexia, as well as limb apraxia but did not have any dysmorphic clinical features. The observations in this family suggest that the phenotypic manifestations of proximal 15q duplications may also involve language-based learning disabilities.

7.84. Blatt, G.J., Fitzgerald, C.M., Guptill, J.T., Booker, A.B., Kemper, T.L., Bauman, M.L. "Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study." *J Autism Dev Disord* 2001 Dec;31(6):537-43.

Neurobiology of Developmental Disorders Laboratory, Department of Anatomy and Neurobiology, Boston University School of Medicine, MA 02118, USA. gblatt@cajal-1.bu.edu

Neuropathological studies in autistic brains have shown small neuronal size and increased cell packing density in a variety of limbic system structures including the hippocampus, a change consistent with curtailment of normal development. Based on these observations in the hippocampus, a series of quantitative receptor autoradiographic studies were undertaken to determine the density and distribution of eight types of neurotransmitter receptors from four neurotransmitter systems (GABAergic, serotonergic [5-HT], cholinergic, and glutamatergic). Data from these single concentration ligand binding studies indicate that the GABAergic receptor system (3[H]-flunitrazepam labeled benzodiazepine binding sites and 3[H]-muscimol labeled GABA(A) receptors) is significantly reduced in high binding regions, marking for the first time an abnormality in the GABA system in autism. In contrast, the density and distribution of the other six receptors studied (3[H]-80H-DPAT labeled 5-HT1A receptors, 3[H]-ketanserin labeled 5-HT2 receptors, 3[H]-pirenzepine labeled M1 receptors, 3[H]-hemicholinium labeled high affinity choline uptake sites, 3[H]-MK801 labeled NMDA receptors, and 3[H]-kainate labeled kainate receptors) in the hippocampus did not demonstrate any statistically significant differences in binding.

7.85. Fatemi, S.H., Stary, J.M., Halt, A.R., Realmuto, G.R. "Dysregulation of Reelin and Bcl-2 proteins in autistic cerebellum." *J Autism Dev Disord* 2001 Dec;31(6):529-35.

Department of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, Minneapolis 55455, USA. fatem002@tc.umn.edu

Autism is a severe neurodevelopmental disorder with potential genetic and environmental causes. Cerebellar pathology including Purkinje cell atrophy has been demonstrated previously. We hypothesized that cell migration and apoptotic mechanisms may account for observed Purkinje cell abnormalities. Reelin is an important secretory

glycoprotein responsible for normal layering of the brain. Bcl-2 is a regulatory protein responsible for control of programmed cell death in the brain. Autistic and normal control cerebellar cortices matched for age, sex, and post-mortem interval (PMI) were prepared for SDS-gel electrophoresis and Western blotting using specific anti-Reelin and anti-Bcl-2 antibodies. Quantification of Reelin bands showed 43%, 44%, and 44% reductions in autistic cerebellum (mean optical density \pm SD per 30 microg protein 4.05 \pm 4.0, 1.98 \pm 2.0, 13.88 \pm 11.9 for 410 kDa, 330 kDa, and 180 kDa bands, respectively; N = 5) compared with controls (mean optical density \pm SD per 30 microg protein, 7.1 \pm 1.6, 3.5 \pm 1.0, 24.7 \pm 5.0; N = 8, $p < 0.0402$ for 180 kDa band). Quantification of Bcl-2 levels showed a 34% to 51% reduction in autistic cerebellum (M \pm SD per 75 microg protein 0.29 \pm 0.08; N = 5) compared with controls (M \pm SD per 75 microg protein 0.59 \pm 0.31; N = 8, $p < 0.0451$). Measurement of beta-actin (M \pm SD for controls 7.3 \pm 2.9; for autistics 6.77 \pm 0.66) in the same homogenates did not differ significantly between groups. These results demonstrate for the first time that dysregulation of Reelin and Bcl-2 may be responsible for some of the brain structural and behavioral abnormalities observed in autism.

7.86. Fahlvik-Planefeldt, C., Herrstrom, P. "Dental care of autistic children within the non-specialized Public Dental Service." *Swed Dent J* 2001;25(3):113-8.

Public Dental Service, Kungsbacka, Sweden. christina.fahlvik-planefeldt@lthalland.se

Children with an autistic disorder may need more dental care and may also be more difficult to treat than healthy children. This study compared oral health in autistic and healthy children. Also explored was the dental management of autistic children within the non-specialized Public Dental Service. The study was designed as a case-control study with all cases of autistic disorders aged 3-19 years identified within a primary care area in southwest Sweden. One dentist did a clinical investigation of cases and one control per case. The patients, or their parents, answered a questionnaire. 28 patients were identified and 20 (71%) agreed to participate in the study. Cases and controls had a similar prevalence of fillings, caries, gingivitis and degree of oral hygiene. However, the need of orthodontic treatment seemed to be greater among the autistic children. According to a standardised assessment, autistic children were less able to cooperate in the dental treatment. Approximately 30% of the cases had occasionally been subjected to specialized dental care. The results of this study indicate that the care provided to autistic children within the non-specialized Public Dental Service is satisfactory, provided that there is access to a paediatric dentist when necessary.

7.87. Magiati, I., Howlin, P. "Monitoring the progress of preschool children with autism enrolled in early intervention programmes: problems in cognitive assessment." *Autism* 2001 Dec;5(4):399-406.

Department of Psychology, St George's Hospital Medical School, London, UK.

This report examines how conclusions about the progress of preschool children enrolled in early intervention programmes may be influenced by the use of different cognitive assessment tools. As part of a longitudinal treatment outcome study, 24 children with autism aged between 27 and 58 months were each tested on the Bayley, Merrill-Palmer and Vineland scales. Their performance on each of these tests was compared. Results showed that, while scores on the different tests were highly correlated, actual test scores varied considerably, with the Bayley tending to produce the lowest IQ scores and the Merrill - Palmer the highly correlated, actual test scores varied considerably, with the Bayley tending to produce the lowest IQ scores and the Merrill-Palmer the highest. These findings have important implications, as it evident that judgements about the effects of therapy may be significantly influenced by the selection of the tests for pre-and post-treatment assessments. Possible ways to collecting, recording and reporting test data, so as to avoid spurious conclusions about treatment effects, are discussed.

7.88. Grant, C.M., Grayson, A., Boucher, J. "Using tests of false belief with children with autism: how valid and reliable are they?" *Autism* 2001 Jun;5(2): 135-45.

University of Sheffield, UK. Cathy. Grant@nottingham.ac.uk

Twenty -two children with autism were given four tests of false belief understanding: the Sally-Anne task, two variants of the deceptive box task, and the three boxes task. The overall consistency of the children's performance was high, 77 percent of the participants either passing or failing all of the tasks. The convergent validity (across-task consistency) of the deceptive box and the three boxes paradigms was high, and the convergent validity of the three boxes and Sally-Anne tasks was also acceptable. However, a weaker level of convergent validity was found for the deceptive box and Sally-Anne tasks, suggesting that these paradigms test slightly different aspects of cognition. The reliability (within-child consistency) of the children's performances across two versions of the deceptive box task was high. These findings are discussed in terms of their practical implications for practitioners and researchers.

7.89. Shah, K. "Research in breif: what do medical students know about autism?" *Autism* 2001 Jun;5(2):127-33.

Psychological Department, St George's Hospital Medical School, London, UK.

Although recent research indicates the importance of early recognition and intervention for children with autism, it is clear that many families remain very dissatisfied with the diagnostic process. In order to improve this situation, it is essential that primary care practitioners, such as GPs, are fully aware of the core symptoms of autism. The present study reports on autism awareness amongst 250 medical students at different stages of their training. Differences between first-year and fourth-year students were compared with respect to their knowledge of various aspects of autism, including diagnosis, cause, symptomatology, treatment and outcome. Fourth-year students were significantly more likely to respond correctly to questions related to diagnostic criteria and core

symptoms. However no significant differences were found between first-year and fourth-year students for other aspects, such as possible causes, IQ profiles, prognosis and treatment. These findings suggest that more emphasis needs to be placed on teaching medical students about autism if diagnosis and access to intervention are to be improved.

7.90. Howlin, P. "Autistic features in Cohen syndrome: a preliminary report." *Dev Med Child Neurol* 2001 Oct;43(10): 692-6. Publication Types: Clinical Trial.

St. George's Hospital Medical School, London, UK.

Cohen syndrome is a rare, genetic, connective-tissue disorder, with the geneticsymptoms of autism and other pervasive developmental disorder (PDDs). METHODS: Twenty-six subjects (5 females, 21 males; ages 3.8 to 23.5 years; mean age 10.1+/-4.8 years) with PDDs (20 with autistic disorder, 1 with Asperger's disorder, 1 with Rett's disorder, and 4 with PDDs not otherwise specified) were treated with open -label mirtazapine (dose range, 7.5-45 mg daily; mean 30.3+/-12.6 mg daily). Twenty had comorbid mental retardation, and 17 were talking concomitant Psychotropic medications. At endpoint, subjects primary caregivers were interviewed using the Clinical Global Impressions (CGI) scale, the Aberrant Behavior Checklist, and a side effect checklist. RESULTS: Twenty-five of 26 subjects completed at least 4 weeks of treatment (mean 150+/-103 days). Nine of 26 subjects (34.6%) were judged responders ("much improved" or "very much improved" on the CGI) based on improvement in a variety of symptoms including aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia. Mirtazapine did not improve core symptoms of social or communication impairment. Adverse effects were minimal and included increased appetite, irritability, and transient sedation. CONCLUSIONS: Mirtazapine was well tolerated but showed only modest effectiveness for treating the associated symptoms of autistic disorder and other PDDs.

7.91. Gray, K.M., Tonge, B.J. "Are there early features of autism in infants and preschool children?" *J Paediatr Child Health* 2001 Jun;37(3):221-6. Publication Types: Review, Review, Tutorial.

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Autism is characterized by impairments in three areas: (i) reciprocal social interaction; (ii) communication; and (iii) repetitive and stereotyped patterns of interest and behaviour. Despite the finding that parents notice abnormalities and problems with their child's development at a very early age, research shows that diagnoses are often made at an age beyond that recommended for the commencement of early intervention. This paper reviews the range of studies that have sought to elucidate the early features of autism in young, preschool children. Impairments in the capacity for reciprocal social interaction involving preverbal, verbal and non-verbal communication, and play and symbolic behaviour are the key features indicative of autism in infants and preschool children.

7.92. Buchsbaum, M.S., Hollander, E., Haznedar, M.M., Tang, C., Spiegel-Cohen, J., Wei, T.C., Solimando, A., Buchsbaum, B.R., Robins, D., Bienstock, C., Cartwright, C., Mosovich, S. "Effect of fluoxetine on regional cerebral metabolism in autistic spectrum disorders: a pilot study." *Int J Neuropsychopharmacol* 2001 Jun;4(2):119-25. Publication Types: Clinical Trial, Controlled Clinical Trial.

Neuroscience PET Laboratory, Mt. Sinai School of Medicine, New York, NY 10029-6574, USA.

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The regional metabolic effects of fluoxetine were examined in patients with autism spectrum disorders. Six adult patients with DSM-IV and Autism Diagnostic Interview (ADI) diagnoses of autism (n = 5) and Asperger's syndrome (n = 1), entered a 16-wk placebo-controlled cross-over trial of fluoxetine. The patients received (18)F-deoxyglucose positron emission tomography with co-registered magnetic resonance imaging at baseline and at the end of the period of fluoxetine administration. After treatment, the patients showed significant improvement on the scores of the Yale-Brown Obsessive-Compulsive Scale - Obsessions subscale and the Hamilton Anxiety Scale; Clinical Global Impressions - Autism scores showed 3 of the patients much improved and 3 unchanged. Relative metabolic rates were significantly higher in the right frontal lobe following fluoxetine, especially in the anterior cingulate gyrus and the orbitofrontal cortex. Patients with higher metabolic rates in the medial frontal region and anterior cingulate when unmedicated were more likely to respond favourably to fluoxetine. These results are consistent with those in depression indicating that higher cingulate gyrus metabolic rates at baseline predict SRI response.

7.93. Groden, J., Diller, A., Bausman, M., Velicer, W., Norman, G., Cautela, J. "The development of a stress survey schedule for persons with autism and other developmental disabilities." *J Autism Dev Disord* 2001 Apr;31(2):207-17. Publication Types: Evaluation Studies.

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The Stress Survey Schedule is an instrument for measuring stress in the lives of persons with autism and other developmental disabilities. Development of the survey and analysis of the underlying measurement structure of the instrument is reported in three studies. Through the use of exploratory and confirmatory analysis procedures, eight dimensions of stress were identified: Anticipation/Uncertainty, Changes and Threats, Unpleasant Events, Pleasant Events, Sensory/Personal Contact, Food Related Activity, Social/Environmental Interactions, and Ritual Related Stress. These stress dimensions are highly relevant to the problems of autism and have not been addressed by other stress surveys. The information obtained from the Stress Survey can be used to plan for strategies to reduce the stress before it occurs or results in maladaptive behavior.

7.94. Purcell, A.E., Rocco, M.M., Lenhart, J.A., Hyder, K., Zimmerman, A.W., Pevsner, J. "Assessment of neural cell adhesion molecule (NCAM) in autistic serum and postmortem brain." *J Autism Dev Disord* 2001 Apr;31(2):183-94.

Department of Neuroscience, Johns Hopkins School of Medicine, Baltimore, Maryland, USA.

Studies have identified structural abnormalities in areas of the autistic brain, with a pattern suggesting that a neurodevelopmental anomaly took place. Neural cell adhesion molecule (NCAM), which is involved in development of the central nervous system, was previously shown to be decreased in the serum of autistic individuals. In the present study, we measured NCAM protein in the sera from controls, patients with autism, siblings of autistic patients, and individuals with other neurologic disorders, but found no significant differences. We also measured NCAM protein in autistic postmortem brain samples and found the longest isoform, NCAM-180, to be significantly decreased. In addition, we investigated the mRNA expression of NCAM in these brain samples using cDNA microarrays and RT-PCR. Results show that NCAM mRNA levels are not altered in autism.

7.95. Bailey, D.B. Jr., Hatton, D.D., Skinner, M., Mesibov, G. "Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome." *J Autism Dev Disord* 2001 Apr;31(2):165-74.

Frank Porter Graham Child Development Center, University of North Carolina at Chapel Hill, 27599, USA.

In the context of a longitudinal study, we assessed the relationship between ratings of autistic behavior, FMR1 protein expression (FMRP), and the developmental trajectories of 55 young males with fragile X syndrome. Autistic behavior, as measured by the Childhood Autism Rating Scale, was not related to FMRP expression. However, autistic behavior was a significant predictor of both developmental status and developmental change. Boys with both autistic behavior and fragile X syndrome functioned at significantly lower levels of development and grew at significantly slower rates than those without autistic behavior. FMRP expression accounted for less variance in developmental level than did autistic behavior, and was not significantly related to slope (developmental change over time). No autistic behavior x FMRP interaction was found.

7.96. Hornig, M., Briese, T., Lipkin, W.I. "Bornavirus tropism and targeted pathogenesis: virus-host interactions in a neurodevelopmental model." *Adv Virus Res* 2001;56:557-82. Publication Types: Review, Review, Academic.

Emerging Diseases Laboratory, Gillespie Neuroscience Research Facility, University of California, Irvine, California 92697, USA.

Animal models provide unique opportunities to explore interactions between host and environment. Two models have been established based on Bornavirus infection that provide new insights into mechanisms by which neurotropic agents

and/or immune factors may impact developing or mature CNS circuitry to effect complex disturbances in movement and behavior. Distinct losses in DA pathways in the adult infection model, and the associated dramatic movement disorder that accompanies it, make it an intriguing model for tardive dyskinesia and dystonic syndromes. The neuropathologic, physiologic, and neurobehavioral features of BDV infection of neonates indicate that it not only provides a useful model for exploring the mechanisms by which viral and immune factors may damage developing neurocircuitry, but also has significant links to the range of biologic, neurostructural, locomotor, cognitive, and social deficits observed in serious neuropsychiatric illnesses such as autism.

7.97. Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E. "The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians." *J Autism Dev Disord* 2001 Feb;31(1):5-17.

Departments of Experimental Psychology and Psychiatry, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom.

Currently there are no brief, self-administered instruments for measuring the degree to which an adult with normal intelligence has the traits associated with the autistic spectrum. In this paper, we report on a new instrument to assess this: the Autism-Spectrum Quotient (AQ). Individuals score in the range 0-50. Four groups of subjects were assessed: Group 1: 58 adults with Asperger syndrome (AS) or high-functioning autism (HFA); Group 2: 174 randomly selected controls. Group 3: 840 students in Cambridge University; and Group 4: 16 winners of the UK Mathematics Olympiad. The adults with AS/HFA had a mean AQ score of 35.8 (SD = 6.5), significantly higher than Group 2 controls (M = 16.4, SD = 6.3). 80% of the adults with AS/HFA scored 32+, versus 2% of controls. Among the controls, men scored slightly but significantly higher than women. No women scored extremely highly (AQ score 34+) whereas 4% of men did so. Twice as many men (40%) as women (21%) scored at intermediate levels (AQ score 20+). Among the AS/HFA group, male and female scores did not differ significantly. The students in Cambridge University did not differ from the randomly selected control group, but scientists (including mathematicians) scored significantly higher than both humanities and social sciences students, confirming an earlier study that autistic conditions are associated with scientific skills. Within the sciences, mathematicians scored highest. This was replicated in Group 4, the Mathematics Olympiad winners scoring significantly higher than the male Cambridge humanities students. 6% of the student sample scored 32+ on the AQ. On interview, 11 out of 11 of these met three or more DSM-IV criteria for AS/HFA, and all were studying sciences/mathematics, and 7 of the 11 met threshold on these criteria. Test-retest and interrater reliability of the AQ was good. The AQ is thus a valuable instrument for rapidly quantifying where any given individual is situated on the continuum from autism to normality. Its potential for screening for autism spectrum conditions in adults of normal intelligence remains to be fully explored.

7.98. Konstantareas, M.M., Hewitt, T. "Autistic disorder and schizophrenia: diagnostic overlaps." *J Autism Dev Disord* 2001 Feb;31(1):19-28.

University of Guelph and Clarke Institute of Psychiatry, Ontario, Canada.

Data on 14 males with autism and 14 with schizophrenia were collected to examine symptom overlap. The Structured Clinical Interview (SCID), the schedule for positive symptoms (SAPS) and the schedule for negative symptoms (SANS) of schizophrenia, the Childhood Autism Rating Scale (CARS), and the DSM-III-R were administered. On the SCID, none of the men with paranoid schizophrenia met criteria for autism while 7 of those with autism met criteria for schizophrenia, disorganized type, showing negative symptoms. In addition, 5 showed positive symptoms on the SAPS and 6 negative symptoms on the SANS. As the difference in measured nonverbal intelligence was not significant, the effects could not be attributed to it. Although the findings continue to support the differentiation of autism and schizophrenia, they are also consistent with a comorbidity of the two disorders, mainly in those diagnosed with autism.

7.99. Woodward, G. "Autism and Parkinson's disease." *Med Hypotheses* 2001 Feb;56(2):246-9.

Department of Neurology, University of Kansas, Kansas City, Kansas, USA.

The pathogenesis of Parkinson's disease, a neurodegenerative disorder, is multifaceted, having a variety of genetic and environmental factors. There is considerable evidence to support the role of toxins, particularly pesticides and herbicides, in at least some of those affected (presumably, mostly the genetically vulnerable). The pathogenesis of autism is no less complex, but little is known about the potential role of toxins for autism, a neurodevelopmental disorder. The incidence of autism appears to be rising, and early exposure to synthetic chemicals is one suspect for this rise. Impaired detoxification of certain chemicals may be common to autism and Parkinson's disease. Further study of environmental influences for either disorder may lead to important insights regarding causation for both, and perhaps for other neurodegenerative and neurodevelopmental disorders as well.

7.100. Todd, R.D. "Probing the nature of child psychopathology." *Child Adolesc Psychiatr Clin N Am* 2001 Apr;10(2):209-24, vii. Publication Types: Review, Review, Tutorial.

Division of Child and Adolescent Psychiatry, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA.

Conceptualizations of the importance and mechanisms of involvement of genetic factors in the etiology of child and adolescent psychopathology are undergoing major changes. In this article, an evolutionary and epidemiologic basis for such changing conceptualizations is outlined. Examples illustrating these principles are drawn from the literature of animal behavior, normal human behavior, autism, and

attention-deficit/hyperactivity disorder. Implications of these findings for both etiologic and treatment studies are proposed.

7.101. Patterson, A., Rafferty, A. "Making it to work: towards employment for the young adult with autism." *Int J Lang Commun Disord* 2001;36 Suppl:475-80.

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In the last few decades there has been an increase in the reported prevalence of autism and its correlates within what is now termed autistic spectrum disorder (ASD): from 20 in every 10,000 children being estimated by Wing and Gould (1979) to 91 in every 10,000 by the National Autistic Society (NAS) (1999). While changes in criteria may account for some of this it is accepted that such children are increasingly being identified and knowledge of autism is growing. Semi-structured interviews were conducted with nine teaching staff from seven different schools for children with special needs to elicit information in relation to preparing young adults with ASD for the world of work. Results indicated educational practices are being modified for children with autism. Currently the most specifically tailored packages are offered in schools for children with severe learning difficulties.

7.102. Bernard, S., Enayati, A., Redwood, L., Roger, H., Binstock, T. "Autism: a novel form of mercury poisoning." *Med Hypotheses* 2001 Apr;56(4):467-71. Publication Types: Review, Review, Academic.

ARC Research, Cranford, New Jersey 07901, USA.

Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children. Copyright 2001 Harcourt Publishers Ltd.

7.103. Chen, R.T., DeStefano, F., Pless, R., Mootrey, G., Kramarz, P., Hibbs, B. "Challenges and controversies in immunization safety." *Infect Dis Clin North Am* 2001 Mar;15(1):21-39, viii. Publication Types: Review, Review, Tutorial.

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No vaccine is perfectly safe or effective. As diseases such as diphtheria and polio fade, vaccine safety concerns, especially alleged links between vaccinations and several chronic illnesses, have become increasingly prominent in the media and to the public. This article reviews the current scientific evidence on several recent vaccine safety controversies. It also provides information on how various safety research is conducted, some of the concurrent challenges, and finally, some guidance on communicating with patients on vaccine risks.

7.104. Gilmore, J.H., van Tol, J.J., Lewis Streicher, H., Williamson, K., Cohen, S.B., Greenwood, R.S., Charles, H.C., Kliewer, M.A., Whitt, J.K., Silva, S.G., Hertzberg, B.S., Chescheir, N.C. "Outcome in children with fetal mild ventriculomegaly: a case series." *Schizophr Res* 2001 Mar 30;48(2-3):219-26.

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Mild enlargement of the lateral ventricles is associated with schizophrenia and other neurodevelopmental disorders. While it has been hypothesized that ventricle abnormalities associated with neurodevelopmental disorders arise during fetal brain development, there is little direct evidence to support this hypothesis. Using ultrasound, it is possible to image the fetal ventricles in utero. Fetal mild ventriculomegaly (MVM) has been associated with developmental delays in early childhood, though longer-term neurodevelopmental outcome has not been studied. Follow-up of five children (aged 4–9 years) with mild enlargement of the lateral ventricles on prenatal ultrasound and two unaffected co-twins is reported: one child had attention deficit hyperactivity disorder (ADHD), one had autism, and two had evidence of learning disorders. These cases suggest that the mild enlargement of the lateral ventricles associated with these neurodevelopmental disorders arises during fetal brain development and can be detected with prenatal ultrasound. In addition, the presence of mildly enlarged, asymmetric ventricles in two children on prenatal ultrasound and on follow-up MRI at age 6 years indicates that ventricle structure present in utero can persist well into childhood brain development. The study of fetal ventricle development with ultrasound may provide important insights into neurodevelopmental disorders and allow the identification of children at high risk.

7.105. Koegel, R.L., Koegel, L.K., McNeerney, E.K. "Pivotal areas in intervention for autism." *J Clin Child Psychol* 2001 Mar;30(1):19-32. Publication Types: Review, Review, Tutorial.

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Discusses several core pivotal areas that appear to be influential in intervention for autism. Literature and outcome data are reviewed with respect to several core areas that appear to be particularly helpful in intervention for autism,

including improving motivation, responsivity to multiple cues, self-management, and self-initiation of social interactions. A conceptual framework is described, and outcome data are reviewed suggesting that when children with autism are motivated to initiate complex social interactions, it may reverse a cycle of impairment, resulting in exceptionally favorable intervention outcomes for many children. Because the peripheral features of autism can be numerous and extensive, the concept of intervention for pivotal areas of functioning may be critical if children are to be habilitated in a time- and cost-efficient manner.

7.106. Mazza, M., De Risio, A., Surian, L., Roncone, R., Casacchia, M. "Selective impairments of theory of mind in people with schizophrenia." *Schizophr Res* 2001 Mar 1;47(2-3):299-308.

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"Theory of mind" (ToM) means the ability to represent others' intentions, knowledge and beliefs and interpret them. Children with autism typically fail tasks aimed at assessing their understanding of false beliefs. These features of autism are strikingly similar to some negative features of schizophrenia. Mental abilities were studied in 35 schizophrenics (DSM-IV) and 17 normal controls. Subjects heard four ToM stories and simultaneously were shown cartoons depicting the action occurring in the stories. All stories involved false beliefs or deception. As for the current symptomatology, schizophrenics were divided according to Liddle's three-dimensional model (reality distortion, psychomotor poverty, disorganisation). Our results show significant differences between schizophrenics and normal controls in all ToM stories, with schizophrenic people performing worse than controls. In first-order stories (a false belief about the state of the world) significant differences were found among symptom dimensions, with the psychomotor poverty group performing worse than disorganisation subjects and reality distortion ones. As for second-order stories (a false belief about the belief of another character), the psychomotor poverty group performed worse than the other groups only in one of the four ToM stories. More research in separating ToM deficits from attention disturbances is needed.

7.107. Slager, S.L., Foroud, T., Haghghi, F., Spence, M.A., Hodge, S.E. "Stoppage: an issue for segregation analysis." *Genet Epidemiol* 2001 Apr;20(3):328-39.

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Segregation analysis assumes that the observed family-size distribution (FSD), i.e., distribution of number of offspring among nuclear families, is independent of the segregation ratio p . However, for certain serious diseases with early onset and diagnosis (e.g., autism), parents may change their original desired family size, based on having one or more affected children, thus violating that assumption. Here we investigate "stoppage," the situation in which such parents have fewer

children than originally planned. Following Brookfield et al. [J Med Genet 25:181-185, 1988], we define a stoppage probability d that after the birth of an affected child, parents will stop having children and thus not reach their original desired family size. We first derive the full correct likelihood for a simple segregation analysis as a function of p , d , and the ascertainment probability π . We show that p can be estimated from this likelihood if the FSD is known. Then, we show that under "random" ascertainment, the presence of stoppage does not bias estimates of p . However, for other ascertainment schemes, we show that is not the case. We use a simulation study to assess the magnitude of bias, and we demonstrate that ignoring the effect of stoppage can seriously bias the estimates of p when the FSD is ignored. In conclusion, stoppage, a realistic scenario for some complex diseases, can represent a serious and potentially intractable problem for segregation analysis. Copyright 2001 Wiley-Liss, Inc.

7.108. Petek, E., Windpassinger, C., Vincent, J.B., Cheung, J., Boright, A.P., Scherer, S.W., Kroisel, P.M., Wagner, K. "Disruption of a novel gene (IMMP2L) by a breakpoint in 7q31 associated with Tourette syndrome." *Am J Hum Genet* 2001 Apr;68(4):848-58.

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Gilles de la Tourette syndrome (GTS) is a complex neuropsychiatric disorder characterized by multiple motor and phonic tics. We identified a male patient with GTS and other anomalies. It was determined that he carried a de novo duplication of the long arm of chromosome 7 [46,XY,dup(7)(q22.1-q31.1)]. Further molecular analysis revealed that the duplication was inverted. The distal chromosomal breakpoint occurred between the two genetic markers D7S515 and D7S522, which define a region previously shown to be disrupted in a familiar case of GTS. Yeast and bacterial artificial chromosome clones spanning the breakpoints were identified by means of FISH analysis. To further characterize the distal breakpoint for a role in GTS, we performed Southern blot hybridization analysis and identified a 6.5-kb *SacI* junction fragment in the patient's genomic DNA. The DNA sequence of this fragment revealed two different breaks in 7q31 within a region of approximately 500 kb. IMMP2L, a novel gene coding for the apparent human homologue of the yeast mitochondrial inner membrane peptidase subunit 2, was found to be disrupted by both the breakpoint in the duplicated fragment and the insertion site in 7q31. The cDNA of the human IMMP2L gene was cloned, and analysis of the complete 1,522-bp transcript revealed that it encompassed six exons spanning 860 kb. The possible role of IMMP2L and several other candidate genes within the region of chromosomal rearrangement, including NRCAM, Leu-Rch Rep, and Reelin, is discussed. The 7q31 breakpoint interval has also been implicated in other neuropsychiatric diseases that demonstrate some clinical overlap with GTS, including autism and speech-language disorder.

7.109. Brune, M. "Social cognition and psychopathology in an evolutionary perspective. Current status and proposals for research." *Psychopathology* 2001 Mar-Apr;34(2):85-94.

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The phylogenetic and ontogenetic developments of social cognition have been a major research focus of evolutionary and developmental psychology. Theory of mind or so-called Machiavellian intelligence, that is the capacity to infer mental states of other individuals and to manipulate them in order to maximise social success, probably emerged due to the need to cope with an increasingly complex social environment. Studies on social reasoning suggest disturbances of mental state attribution in psychiatric disorders. However, apart from autism spectrum disorders, the systematic evaluation of social cognition is still in its infancy, and the present data are ambiguous due to methodological difficulties. Based on the concept of the modular organisation of the mind, a stepwise investigation of social cognition in psychiatric disorders is proposed, including clinical description and available standardised methods. The specific characteristics of psychiatric disorders in respect of social cognition, therefore, may vary according to the hierarchical organisation of the social module. Systematic studies on social reasoning processes in psychiatric disorders may provide new insights also useful for the development of coping strategies in cognitive-behavioural therapy. Copyright 2001 S. Karger AG, Basel

7.110. Tager-Flusberg, H., Joseph, R., Folstein, S. "Current directions in research on autism." *Ment Retard Dev Disabil Res Rev* 2001;7(1):21-9. Publication Types: Review, Review, Tutorial.

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One of the most active areas of current research in the field of developmental disorders is autism. Since the NIH State of the Science conference, held in 1995 (Bristol et al. [1996] *J. Autism Dev. Disorders* 26:121-154), funding opportunities for comprehensive research programs addressing genetic, neurobiological, and behavioral aspects of this complex disorder have grown exponentially. Although we are far from having a complete understanding of the causes and deficits that define autism, significant progress has been made over the past few years. In this review, we summarize recent developments across a number of different areas of research in the field of autism, including diagnosis; defining the phenotypic features in individuals with autism; genetic bases; and neurobiological deficits. Copyright 2001 Wiley-Liss, Inc.

7.111. Trevarthen, C., Aitken, K.J. "Infant intersubjectivity: research, theory, and clinical applications." *J Child Psychol Psychiatry* 2001 Jan;42(1):3-48. Publication Types: Review, Review, Tutorial.

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We review research evidence on the emergence and development of active “self-and-other” awareness in infancy, and examine the importance of its motives and emotions to mental health practice with children. This relates to how communication begins and develops in infancy, how it influences the individual subject’s movement, perception, and learning, and how the infant’s biologically grounded self-regulation of internal state and self-conscious purposefulness is sustained through active engagement with sympathetic others. Mutual self-other-consciousness is found to play the lead role in developing a child’s cooperative intelligence for cultural learning and language. A variety of preconceptions have animated rival research traditions investigating infant communication and cognition. We distinguish the concept of “intersubjectivity”, and outline the history of its use in developmental research. The transforming body and brain of a human individual grows in active engagement with an environment of human factors—organic at first, then psychological or inter-mental. Adaptive, human-responsive processes are generated first by interneuronal activity within the developing brain as formation of the human embryo is regulated in a support-system of maternal tissues. Neural structures are further elaborated with the benefit of intra-uterine stimuli in the foetus, then supported in the rapidly growing forebrain and cerebellum of the young child by experience of the intuitive responses of parents and other human companions. We focus particularly on intrinsic patterns and processes in pre-natal and post-natal brain maturation that anticipate psychosocial support in infancy. The operation of an intrinsic motive formation (IMF) that developed in the core of the brain before birth is evident in the tightly integrated intermodal sensory-motor coordination of a newborn infant’s orienting to stimuli and preferential learning of human signals, by the temporal coherence and intrinsic rhythms of infant behaviour, especially in communication, and neonates’ extraordinary capacities for reactive and evocative imitation. The correct functioning of this integrated neural motivating system is found to be essential to the development of both the infant’s purposeful consciousness and his or her ability to cooperate with other persons’ actions and interests, and to learn from them. The relevance of infants’ inherent intersubjectivity to major child mental health issues is highlighted by examining selected areas of clinical concern. We review recent findings on postnatal depression, prematurity, autism, ADHD, specific language impairments, and central auditory processing deficits, and comment on the efficacy of interventions that aim to support intrinsic motives for intersubjective communication when these are not developing normally.

7.112. Cowan, W.M., Kandel, E.R. “**Prospects for neurology and psychiatry.**” *JAMA* 2001 Feb 7;285(5):594-600.

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Neurological and psychiatric illnesses are among the most common and most serious health problems in developed societies. The most promising advances in neurological and

psychiatric diseases will require advances in neuroscience for their elucidation, prevention, and treatment. Technical advances have improved methods for identifying brain regions involved during various types of cognitive activity, for tracing connections between parts of the brain, for visualizing individual neurons in living brain preparations, for recording the activities of neurons, and for studying the activity of single-ion channels and the receptors for various neurotransmitters. The most significant advances in the past 20 years have come from the application to the nervous system of molecular genetics and molecular cell biology. Discovery of the monogenic disorder responsible for Huntington disease and understanding its pathogenesis can serve as a paradigm for unraveling the much more complex, polygenic disorders responsible for such psychiatric diseases as schizophrenia, manic depressive illness, and borderline personality disorder. Thus, a new degree of cooperation between neurology and psychiatry is likely to result, especially for the treatment of patients with illnesses such as autism, mental retardation, cognitive disorders associated with Alzheimer and Parkinson disease that overlap between the 2 disciplines.

7.113. Korkmaz, B. “**Infantile autism: adult outcome.**” *Semin Clin Neuropsychiatry* 2000 Jul;5(3):164-70. Publication Types: Review, Review, Tutorial.

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Although the core features of autism do not change qualitatively, a gradual overall symptomatic improvement including an increase in adaptive skills is observed in most cases with age. Follow-up studies show that the diagnostic features, the differential diagnosis, and clinical problems of adult autistics differ substantially from that of autistic children. The differential diagnosis of older autistics include personality disorders, learning disabilities, and mood disorder. Depression, epilepsy, and behavioral problems such as aggression and agitation may be major clinical problems during adolescence. The early indicators of a better outcome include a higher level of IQ and language. Among the neuropsychological variables, measures of flexibility and cognitive shift are important as prognostic factors. Early behavioral and educational intervention may especially increase the adaptive skills of the patients and promote the in-family communication. The outcome studies of autism are particularly helpful in addressing the appropriate and most effective programs of remediation for adult autistics.

7.114. Jacobson, J.W., Mulick, J.A. “**System and cost research issues in treatments for people with autistic disorders.**” *J Autism Dev Disord* 2000 Dec;30(6):585-93. Publication Types: Review, Review, Tutorial.

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Parents of children with autism and pervasive developmental disorder and educational and clinical practitioners providing services to them regularly confront a wide range of service selection and financial decisions that are not as yet effectively

addressed by applied research. Relevant systems issues span a very broad range of concerns: (a) systems delivery models and issues (e.g., costs of services, implementation of intensive intervention, and teacher or therapist training); (b) how best to integrate treatments; (c) providing treatment to those with limited monetary resources; (d) cost and cost/benefit analyses; (e) how to educate adult psychiatrists (as well as other practitioners and personnel) regarding autism; and (f) gaps between research and practice.

7.115. Aylott, J. "Understanding children with autism: exploding the myths." *Br J Nurs* 2000 Jun 22-Jul 12;9(12):779-84. Publication Types: Review, Review Literature.

Sheffield Hallam University and Academic.

The incidence of autism is increasing in both the USA and in Britain. There is still controversy over what causes autism and even greater controversy over selecting a preferred method of intervention and support (as there is no treatment for autism). Although there is now a general consensus that individuals may have a genetic predisposition to develop autism, it is also acknowledged that this may be offset by a range of environmental and/or biological factors. The understanding of the causation of autism is now considered in much the same way as we understand cerebral palsy, in that there can be a range of different reasons for causation and prevalence. This article, the first of two parts, will explore how an awareness and understanding of autism can enable nurses working with children with autism to provide more child-centred nursing care based on fact as opposed to stereotype and mythology surrounding autism. The second part will concentrate on adults with autism.

7.116. Garrett, J.M., Bird, S.J. "Ethical issues in communicating science." *Sci Eng Ethics* 2000 Oct;6(4):435-42. Publication Types: Editorial.

Most of the publicized work on scientific ethics concentrates on establishing professional norms and avoiding misconduct. The successful communication of science is the responsibility of all involved in the process. In one study, the increased incidence of autism and other social developmental disorders in males was investigated by examining individuals with Turner's syndrome (XO females). In the national newspaper this became "Genetic X-factor explains why boys will always be boys". The steps by which a study on developmental disorders, published in a highly prestigious journal, was transformed into an article in the science section which 'explained' the socially expected gender-based behavior of genetically normal children are fascinating and, unfortunately far too typical. The scientists wrote an excellent article that has just one sentence at the end that hesitantly suggests that the findings might, with further study, have some relevance to understanding normal behavior. The general interest article in the front of the journal gave a good account of the research, but suggested more strongly that there could be an in-built biological dimorphism in social cognition. This was misrepresented in the press as proof of gender differences that "undermines the trend towards sexual equality", and both illustrates cultural bias and provides fodder for feminist

critiques of science. The study has been made to appear to be biased in favor of justifying the social structure of society, and yet it was the translation from the scientific study to national news that produced this transformation to biased genetic determinism. It is poor communication of the actual science, coupled with a lack of skepticism on the part of the public, that contributes to such a misapplication of science. Scientists should resist the urge to generalize their results to make them more compelling. The science community should not allow misconstructions of scientific facts to go unchallenged. Journalists, for both the scientific publication and the newspaper, should resist the inclination to embellish the finding with social significance that is not present. For their part, readers must be doubly skeptical of any finding that appears to underwrite any current social hierarchy. We are all responsible for a communication and interpretation of science that is as accurate and socially responsible as possible.

7.117. Hulland, S., Sigal, M.J. "Hospital-based dental care for persons with disabilities: a study of patient selection criteria." *Spec Care Dentist* 2000 Jul-Aug;20(4):131-8.

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The objective of this investigation was to generate a medical and dental profile of patients attending the Mount Sinai Hospital Dental Program for Persons with Disabilities, to determine if certain selected criteria could identify patients likely to require dental care in that setting. The need for dental care under general anesthesia was used as the prime indicator that care should be provided in a hospital setting. A retrospective review of all the charts of the patients enrolled in this hospital program was undertaken. Results indicated that patients who were treated in this hospital-based dental program had the following characteristics: moderate to profound mental retardation (39.5%), moderate to severe behavioral problems (31.1%), and/or a history of seizure activity (29.1%). Behavioral criteria appear to be the predominant reason for the provision of hospital-based dental care for persons with disabilities.

7.118. Szatmari, P., Bryson, S.E., Streiner, D.L., Wilson, F., Archer, L., Rye, C. "Two-year outcome of preschool children with autism or Asperger's syndrome." *Am J Psychiatry* 2000 Dec;157(12):1980-7.

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OBJECTIVE: DSM-IV specifies that Asperger's disorder is a type of pervasive developmental disorder without clinically significant cognitive or language delay. There are no data, however, on the outcome of children with Asperger's disorder or on whether their outcome differs from that of children with autism. The objectives of this study were to compare the outcome of groups of children with these disorders over a period of 2 years on variables independent of the defining criteria and to identify variables that might account for these differences. **METHOD:** All children 4-6 years of age who came

for assessment or were currently in treatment at a pervasive developmental disorder service of one of several centers in a large geographic region were identified. Children who received a diagnosis of autism (N=46) or Asperger's syndrome (N=20) on the basis of a diagnostic interview and had an IQ in the nonretarded range were given a battery of cognitive, language, and behavioral tests. Families were contacted roughly 2 years after the date of their enrollment in the study, and many of the tests were readministered. **RESULTS:** Children with Asperger's syndrome had better social skills and fewer autistic symptoms 2 years after study enrollment than the children with autism. The differences in outcome could not be explained by initial differences in IQ and language abilities. Children with autism who had developed verbal fluency at follow-up were very similar to the children with Asperger's syndrome at study enrollment. **CONCLUSIONS:** Although the exact mechanism for the differences in outcome remain to be determined, it appears that Asperger's disorder and autism represent parallel but potentially overlapping developmental trajectories.

7.119. Kielinen, M., Linna, S.L., Moilanen, I. "Autism in Northern Finland." *Eur Child Adolesc Psychiatry* 2000 Sep;9(3):162-7.

Department of Pediatrics, Clinic of Child Psychiatry, University of Oulu, Finland.

Recent research reports show that autistic spectrum disorders may actually be more common than previously believed. General awareness and clinical knowledge of these disorders have increased, and the criteria in the ICD-10 and the DSM-IV are also now more detailed. The diagnostic criteria and the methods of ascertainment influence the prevalence. The age specific incidence obtained in this study showed the cumulative incidence to be lowest, 6.1 per 10,000, in the oldest age group of 15- to 18-year-old children, and highest, 20.7 per 10,000, in the age group of 5-7 year-olds, when the criteria of the ICD-10 and the DSM-IV were used. In this study, almost 50% of the autistic cases had a tested IQ above 70. The degree of autism, as assessed by the Childhood Autism Rating Scale (CARS), varied from mild autistic features in 8.5% through moderate in 58.5% to severe in 33.0%.

7.120. Wolk, L., Giesen, J. "A phonological investigation of four siblings with childhood autism." *J Commun Disord* 2000 Sep-Oct;33(5):371-89.

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Multiple autistic siblings of four or more are extremely rare. This study carried out a phonological investigation of four siblings in a unique family. Phonological investigations were carried out on four siblings with childhood autism (one female and three males). In addition, behavioral characteristics were described and compared among the four children. The two methods used for speech elicitation were object naming and spontaneous speech utterances. Data analyses included phonetic inventory and phonological process analyses. Phonological investigations showed that these autistic

children, at least the more severely impaired ones, do not only exhibit delayed phonological behavior, but also show some atypical patterns that rarely occur in normal development. Findings from this study reveal five general patterns of phonological behavior, namely: (a) evidence of several phonological processes that are common in normal development; (b) persistence of several phonological processes, such as labialization, cluster reduction, or final consonant deletion, beyond the expected age; (c) evidence of unusual sound changes, such as extensive segment coalescence, frication of liquids, and velarization; (d) evidence of "chronological mismatch" (Grunwell, 1981), which is the notion of the absence of earlier sounds co-occurring with characteristics of later development; and (e) restricted use of contrasts. These findings support earlier work on a single autistic child using phonological investigations (Wolk & Edwards, 1993), but contrast with all previous research suggesting that autistic children exhibit delayed rather than unusual phonological development. Clinical implications are suggested.

7.121. Ghaziuddin, M. "Autism in Down's syndrome: a family history study." *J Intellect Disabil Res* 2000 Oct;44 (Pt 5):562-6.

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Several recent reports have described the occurrence of autism in subjects with Down's syndrome (DS). However, relatively little is known about the family history of these subjects, especially with reference to autism. In order to address this issue, the present author examined 11 subjects with DS and autism (DSM-III-R; nine males), and compared them with seven controls with DS but without autism (DSM-III-R; three males). Details about family psychiatric history were obtained from both groups with an emphasis on autism and related disorders. Subjects with both DS and autism had an excess of first-degree relatives who met the description of the broader phenotype of autism. Seven (64%) of the subjects with autism had an affected parent as against one (14%) of the control group. Similarly, four out of 11 siblings (36%) in the DS with autism group showed features suggestive of the broader autistic phenotype compared to none in the control group. These findings suggest that, at least in some cases, autism-specific genetic factors may be important even when autism occurs in the presence of known medical conditions. Further studies of the mechanism of comorbidity of autism with medical conditions may help clarify the aetiology of the disorder.

7.122. Stotz-Ingenlath, G. "Epistemological aspects of Eugen Bleuler's conception of schizophrenia in 1911." *Med Health Care Philos* 2000;3(2):153-9. Publication Types: Biography, Historical Article. Personal Name as Subject: Bleuler E.

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Eugen Bleuler, in 1911, renamed the group of mental disorders with poor prognosis which Emil Kraepelin had called

"dementia praecox" "group of schizophrenias", because for him the splitting of personality was the main symptom. Biographical, scientific and methodological influences on Bleuler's concept of schizophrenia are shown with special reference to Kraepelin and Freud. Bleuler was a passionate and very experienced clinician. He lived with his patients, taking care of them and writing down his observations. Methodologically he was an empiricist and an eclecticist with a wide reading knowledge. In an impaired association of ideas, in disordered affectivity, in marked ambivalence and autism Bleuler saw the main symptoms of schizophrenia. For him these so-called pathological phenomena actually seemed to be only exaggerations of normal psychic functions. So there were only a quantitative, not a qualitative difference between schizophrenia and normal psychic processes and studies on schizophrenic "pathology" — seen as a disturbance, not as a disease — might analogously illustrate normal psychic reactions and vice versa. In etiology as well as in therapy Bleuler took into account psychological and (neuro)physiological (somatic) mechanisms — thus combining organicism and dynamic psychiatry and coming very close to modern concepts, e.g. the one of stress and vulnerability. Bleuler's main merit is the stressing on an idiographic "understanding" of the patient and a plausible and subtle explanation of schizophrenia which helped to reduce the alienation of the affected persons.

7.123. Bugge, M., Bruun-Petersen, G., Brondum-Nielsen, K., Friedrich, U., Hansen, J., Jensen, G., Jensen, P.K., Kristoffersson, U., Lundsteen, C., Niebuhr, E., Rasmussen, K.R., Rasmussen, K., Tommerup, N. **"Disease associated balanced chromosome rearrangements: a resource for large scale genotype-phenotype delineation in man."** *J Med Genet* 2000 Nov;37(11):858-65.

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Disease associated balanced chromosomal rearrangements (DBCRs), which truncate, delete, or otherwise inactivate specific genes, have been instrumental for positional cloning of many disease genes. A network of cytogenetic laboratories, Mendelian Cytogenetics Network (MCN), has been established to facilitate the identification and mapping of DBCRs. To get an estimate of the potential of this approach, we surveyed all cytogenetic archives in Denmark and southern Sweden, with a population of approximately 6.6 million. The nine laboratories have performed 71 739 postnatal cytogenetic tests. Excluding Robertsonian translocations and chromosome 9 inversions, we identified 216 DBCRs (approximately 0.3%), including a minimum estimate of 114 de novo reciprocal translocations (0.16%) and eight de novo inversions (0.01%). Altogether, this is six times more frequent than in the general population, suggesting a causal relationship with the traits involved in most of these cases. Of the identified cases, only 25 (12%) have been published, including 12 cases with known syndromes and 13 cases with unspecified mental retardation/congenital malformations. The remaining DBCRs were associated with a plethora of traits including mental

retardation, dysmorphic features, major congenital malformations, autism, and male and female infertility. Several of the unpublished DBCRs defined candidate breakpoints for nail-patella, Prader-Willi, and Schmidt syndromes, ataxia, and ulna aplasia. The implication of the survey is apparent when compared with MCN; altogether, the 292 participating laboratories have performed >2.5 million postnatal analyses, with an estimated approximately 7500 DBCRs stored in their archives, of which more than half might be causative mutations. In addition, an estimated 450-500 novel cases should be detected each year. Our data illustrate that DBCRs and MCN are resources for large scale establishment of phenotype-genotype relationships in man.

7.124. Geckeler, A.S., Libby, M.E., Graff, R.B., Ahearn, W.H. **"Effects of reinforcer choice measured in single-operant and concurrent-schedule procedures."** *J Appl Behav Anal* 2000 Fall;33(3):347-51.

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The effects of choice and no choice of reinforcer on the response rates of 3 children with autism were compared across single-operant and concurrent-schedule procedures. No consistent differences in responding between choice and no-choice components emerged during single-operant phases. During the concurrent-schedule phases, however, all participants had substantially higher rates of responding to the button that led to a choice among reinforcers than to the button that did not lead to choice.

7.125. Bowler, D.M., Briskman, J.A. **"Photographic cues do not always facilitate performance on false belief tasks in children with autism."** *J Autism Dev Disord* 2000 Aug;30(4):305-16.

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Previous studies have indicated that a pictorial representation of a prior belief can help 3-year-old children (Mitchell & Lacohee, 1991) as well as children with autism (Charman & Lynggaard, 1998) to pass false belief tasks that used the deceptive box or "Smarties" paradigm. The studies reported here attempted to replicate these findings using the unexpected transfer or "Sally-Anne" paradigm, which requires children to predict the actions of a protagonist on the basis of a false belief. Results showed no facilitative effect on "Sally-Anne" task performance for the children with autism or for comparison children of either representational or nonrepresentational cues. This effect was found even in children who benefited from the intervention with the deceptive box paradigm. The findings raise issues regarding the way false belief tasks are conceptualized by experimenters and the demands different false belief paradigms make on children.

7.126. Tanguay, P.E. **"Pervasive developmental disorders: a 10-year review."** *J Am Acad Child Adolesc Psychiatry* 2000. Publication Types: Review, Review, Tutorial.

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OBJECTIVE: To summarize recent advances about the nature, diagnosis, and treatment of pervasive developmental disorders. **METHOD:** Review of Medline databases, books, and book chapters published between July 1989 and November 1999. **RESULTS:** Clinical and genetic studies support expansion of the concept of autism to include a broader spectrum of social communication handicaps. The prevalence of autism is approximately 1 per 2,000; the prevalence of autism and Asperger's disorder together is 1 per 1,000. The Checklist for Autism in Toddlers is a useful screening instrument for 18-month-old children; the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule are instruments of choice for research. Although twin and family studies clearly support genetic factors as important in autism, linkage analysis studies indicate that many genes may be involved. There is no one treatment of choice. Social-pragmatic approaches, augmented by individualized strategies and social coaching, may be best for teaching social communication skills. Pharmacological interventions have a limited role in improving social communication, but selective serotonin reuptake inhibitors and atypical neuroleptic medications may help ameliorate aggression, hyperactivity, and other secondary problems. **CONCLUSIONS:** Private and government agencies must continue to support basic and applied research.

7.127. O'Riordan, M. "Superior modulation of activation levels of stimulus representations does not underlie superior discrimination in autism." *Cognition* 2000 Nov 16;77(2):81-96. Publication Types: Clinical Trial, Randomized Controlled Trial.

Department of Experimental Psychology, University of Cambridge, Downing Street, CB2 3EB, Cambridge, UK. mafo100@cus.cam.ac.uk

The performance of children with and without autism was compared in object-based positive and negative priming tasks within a visual search procedure. Object-based positive and negative priming effects were found in both groups of children. This result provides the first evidence for the activation of object-based representations during visual search task performance and further supports the notion that both excitatory and inhibitory guidance mechanisms are involved in target location in visual search. The children with autism were overall better than the typically developing children at visual search, thus replicating demonstrations of superior discrimination in autism. Furthermore, there was no difference between the magnitude of the positive nor the negative priming effects of the groups. This finding suggests that excitatory and inhibitory control operate comparably in autism and normal development. These results are discussed in the light of the superior ability of individuals with autism to discriminate between items. More specifically, it is argued that superior discrimination in autism does not result from enhanced top-down excitatory and inhibitory control.

7.128. Diesfeld, K. "Neither consenting nor protesting: an ethical analysis of a man with autism." *J Med Ethics* 2000 Aug;26(4):277-81. Publication Types: Legal Cases.

University of Kent, Canterbury. kdiesfeld@hotmail.com

This article critically examines the 25 June 1998 decision by the House of Lords regarding the psychiatric admission of a man with autism. Mr L was able neither to consent to, nor refuse, that admission and the disposition of his case illuminates the current debate regarding best interests of vulnerable adults by the judiciary and the psychiatric profession. This article begins with the assumption that hospitalisation was not the optimum response to Mr L's condition, provides alternative approaches to the interpretation of best interest and examines principles of liberty, anti-discrimination, and equal protection.

7.129. Manning, J.T., Bundred, P.E. "The ratio of 2nd to 4th digit length: a new predictor of disease predisposition?" *Med Hypotheses* 2000 May;54(5):855-7.

School of Biological Sciences, University of Liverpool, Liverpool, UK. jtmann@liv.ac.uk

The ratio between the length of the 2nd and 4th digits is: (a) fixed in utero; (b) lower in men than in women; (c) negatively related to testosterone and sperm counts; and (d) positively related to oestrogen concentrations. Prenatal levels of testosterone and oestrogen have been implicated in infertility, autism, dyslexia, migraine, stammering, immune dysfunction, myocardial infarction and breast cancer. We suggest that 2D:4D ratio is predictive of these diseases and may be used in diagnosis, prognosis and in early life-style interventions which may delay the onset of disease or facilitate its early detection. Copyright 2000 Harcourt Publishers Ltd.

7.130. Stevens, M.C., Fein, D.H., Waterhouse, L.H. "Season of birth effects in autism." *J Clin Exp Neuropsychol* 2000 Jun;22(3):399-407.

Department of Psychiatry, University of Connecticut Health Center, Farmington, CT 06030-2103, United States of America. stevens@psychiatry.uchc.edu

This study examined a sample of preschool-age children with autism in an attempt to identify patterns of birth dates that deviated from expected frequencies by month or season. Birth dates of children with autism and those of a non-autistic sibling control group were compared to the number of total live births gathered from U.S. Census data. Analyses included two types of chi-square analyses and a seasonal harmonic trend analysis. Previously unmentioned in the literature is a seasonal effect finding for females within the entire sample, and both a seasonal and monthly effect for children classified as socially Passive by the Wing system. A significant elevation was also found in March within the Boston sub-sample (n = 37). This sample largely comprised low-functioning boys with autism, a finding consistent with previous findings in the literature. Peri-natal complications and early life development of the subjects from the Boston site are detailed.

7.131. Partington, M., Mowat, D., Einfeld, S., Tonge, B., Turner, G. "Genes on the X chromosome are important in undiagnosed mental retardation." *Am J Med Genet* 2000 May 1;92(1):57-61.

Hunter Genetics, The Hunter Area Health Service, Newcastle, New South Wales, Australia. parturn@ozemail.com.au

The clinical genetic diagnosis was reviewed in 429 subjects with intellectual disability in the Australian Child and Adolescent Development (ACAD) study of behavioural problems. With minor differences, the overall "general distribution by causation" was similar to that found by the Consensus Conference of the American College of Medical Genetics in 1995. There was a significant male excess in the whole series which was shown to reside in those with "autism," those with undiagnosed nonsyndromic mental retardation (NSMR) and those with X-linked monogenic disorders. It is argued that a substantial proportion of undiagnosed NSMR is caused by genes on the X chromosome. Some of the practical problems of assigning individuals to diagnostic groups are discussed. Copyright 2000 Wiley-Liss, Inc.

7.132. Mundy, P., Card, J., Fox, N. "EEG correlates of the development of infant joint attention skills." *Dev Psychobiol* 2000 May;36(4):325-38.

Department of Psychology, University of Miami, Miami, FL 33146, USA.

The development of the capacity for social attention coordination, or "joint attention," is a major milestone of infancy. Data from a recent study of handicapped infants have raised the hypothesis that the tendency to initiate bids for joint attention may reflect processes associated with the frontal cortex to a greater extent than other forms of infant attention coordination (R. Caplan et al., 1993). This hypothesis was examined in a longitudinal study of 32 normally developing infants. The results indicated that EEG data at 14 months indicative of left frontal, as well as left and right central cortical activity, was associated with the tendency to initiate joint attention bids (IJA) at 14 and 18 months. In contrast, a pattern of left parietal activation and right parietal deactivation at 14 months was associated with the development of the capacity to respond to the joint attention bids (RJA) of others at 14 and 18 months. These results were interpreted to be consistent with a general anterior-posterior model of attention development (M. Posner & S. Petersen, 1990). The implications of these results for current conceptualizations of joint attention development, as well as for understanding the disturbance of joint attention skill development in autism are discussed. Copyright 2000 John Wiley & Sons Inc.

7.133. Lingarde, B., Jonsson, S.A., Luts, A., Brun, A. "Cerebellar abnormalities in mental illness. A study on Purkinje cell density in schizophrenic men." *Eur Child Adolesc Psychiatry* 2000 Mar;9(1):21-5.

Department of Clinical Neuroscience, University Hospital, Lund.

The linear Purkinje cell density in the cerebellar vermis was investigated in a small cohort of adult onset schizophrenic men with well-documented hippocampal abnormalities. There were no differences in comparison with age-matched controls. This negative finding indicates that vermian abnormalities undoubtedly seen in some schizophrenic patients may constitute a subsyndrome, possibly related to autistic disorders in which cerebellar abnormalities are well corroborated.

7.134. Pilowsky, T., Yirmiya, N., Arbelle, S., Mozes, T. "Theory of mind abilities of children with schizophrenia, children with autism, and normally developing children." *Schizophr Res* 2000 Apr 7;42(2):145-55.

Hebrew University of Jerusalem, Jerusalem, Israel.

Theory of mind (ToM) abilities of children with schizophrenia, children with high functioning autism, and normally developing children, matched on mental age (MA), verbal MA, and performance MA, were compared. Both clinical groups were matched on chronological age as well, whereas the normally developing children were younger. A fact belief task, a value belief task, a deception task, and a false belief task were administered. The three groups did not differ on the fact belief task. Children with autism performed more poorly than normally developing children on value belief and false belief tasks, and more poorly than individuals with schizophrenia on the deception task. Children with schizophrenia performed more poorly than normally developing children only on the false belief task. Overall, the group with autism passed significantly fewer tasks compared to the normally developing group. ToM abilities correlated with verbal abilities for individuals with autism. The ToM abilities of children with paranoid schizophrenia and children with undifferentiated or disorganized schizophrenia did not differ. Findings strengthen the notion of a limited understanding of ToM in schizophrenia, and support the notion that ToM deficits, although more severe in autism, are not unique to autism.

7.135. DeLeon, I.G., Fisher, W.W., Herman, K.M., Crosland, K.C. "Assessment of a response bias for aggression over functionally equivalent appropriate behavior." *J Appl Behav Anal* 2000 Spring;33(1):73-7.

Kennedy Krieger Institute and Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.

We evaluated the effects of a dense (fixed-ratio 1) schedule of reinforcement for an 11-year-old boy's mands for toys while aggression produced the same toys on various schedules chosen on the basis of a progressive-ratio probe. Based on the probe session data, we accurately predicted that aggression would be more probable than mands when the schedules were equal or slightly discrepant, but that mands would be more probable when the schedule discrepancy was large.

7.136. Brown, K.A., Wacker, D.P., Derby, K.M., Peck, S.M., Richman, D.M., Sasso, G.M., Knutson, C.L., Harding, J.W. "Evaluating the effects of functional communication training in the presence and absence of establishing operations." *J Appl Behav Anal* 2000 Spring;33(1):53-71.

The University of Iowa, USA.

We conducted functional analyses of aberrant behavior with 4 children with developmental disabilities. We then implemented functional communication training (FCT) by using different mands across two contexts, one in which the establishing operation (EO) that was relevant to the function of aberrant behavior was present and one in which the EO that was relevant to the function of aberrant behavior was absent. The mand used in the EO-present context served the same function as aberrant behavior, and the mand used in the EO-absent context served a different function than the one identified via the functional analysis. In addition, a free-play (control) condition was conducted for all children. Increases in relevant manding were observed in the EO-present context for 3 of the 4 participants. Decreases in aberrant behavior were achieved by the end of the treatment analysis for all 4 participants. Irrelevant mands were rarely observed in the EO-absent context for 3 of the 4 participants. Evaluating the effectiveness of FCT across different contexts allowed a further analysis of manding when the establishing operations were present or absent. The contributions of this study to the understanding of functional equivalence are also discussed.

7.137. Thony, B., Auerbach, G., Bläu, N. "Tetrahydrobiopterin biosynthesis, regeneration and functions." *Biochem J* 2000 Apr 1;347 Pt 1:1-16. Publication Types: Review, Review, Academic.

Division of Clinical Chemistry, University Children's Hospital, Steinwiesstrasse 75, 8032 Zurich, Switzerland.

Tetrahydrobiopterin (BH(4)) cofactor is essential for various processes, and is present in probably every cell or tissue of higher organisms. BH(4) is required for various enzyme activities, and for less defined functions at the cellular level. The pathway for the de novo biosynthesis of BH(4) from GTP involves GTP cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase and sepiapterin reductase. Cofactor regeneration requires pterin-4a-carbinolamine dehydratase and dihydropteridine reductase. Based on gene cloning, recombinant expression, mutagenesis studies, structural analysis of crystals and NMR studies, reaction mechanisms for the biosynthetic and recycling enzymes were proposed. With regard to the regulation of cofactor biosynthesis, the major controlling point is GTP cyclohydrolase I, the expression of which may be under the control of cytokine induction. In the liver at least, activity is inhibited by BH(4), but stimulated by phenylalanine through the GTP cyclohydrolase I feedback regulatory protein. The enzymes that depend on BH(4) are the phenylalanine, tyrosine and tryptophan hydroxylases, the latter two being the rate-limiting enzymes for catecholamine and 5-hydroxytryptamine (serotonin) biosynthesis, all NO synthase isoforms and the glyceryl-ether mono-oxygenase. On a cellular level, BH(4) has been found to be a growth or

proliferation factor for *Crithidia fasciculata*, haemopoietic cells and various mammalian cell lines. In the nervous system, BH(4) is a self-protecting factor for NO, or a general neuroprotecting factor via the NO synthase pathway, and has neurotransmitter-releasing function. With regard to human disease, BH(4) deficiency due to autosomal recessive mutations in all enzymes (except sepiapterin reductase) have been described as a cause of hyperphenylalaninaemia. Furthermore, several neurological diseases, including Doparesponsive dystonia, but also Alzheimer's disease, Parkinson's disease, autism and depression, have been suggested to be a consequence of restricted cofactor availability.

7.138. Kim, S.J., Veenstra-VanderWeele, J., Hanna, G.L., Gonen, D., Leventhal, B.L., Cook, E.H. Jr. "Mutation screening of human 5-HT(2B)receptor gene in early-onset obsessive-compulsive disorder." *Mol Cell Probes* 2000 Feb;14(1):47-52.

Laboratory of Developmental Neuroscience, Child and Adolescent Psychiatry, Department of Psychiatry MC3077, 5841 S Maryland Avenue, Chicago, IL 60637, USA.

The serotonin receptor 2B gene (HTR2B; MIM 601122) is a pharmacological and positional candidate gene in early-onset obsessive-compulsive disorder. Sequences of a putative promoter region and splice regions were first elucidated, then sequenced along with HTR2B coding regions. Proband from seven families included in a previous genome scan in which one of the strongest linkage findings was to a region including HTR2B, along with two genomic DNA pools of 10 unrelated control subjects and 10 unrelated autism probands were screened. One single nucleotide polymorphism was found in intron 1, that may be useful as a marker in genetic linkage and association studies. It does not appear likely to affect splicing. No evidence for functional mutation was found in the sequenced regions of HTR2B. Copyright 2000 Academic Press.

7.139. Stevens, M.C., Fein, D.A., Dunn, M., Allen, D., Waterhouse, L.H., Feinstein, C., Rapin, I. "Subgroups of children with autism by cluster analysis: a longitudinal examination." *J Am Acad Child Adolesc Psychiatry* 2000 Mar;39(3):346-52.

Department of Psychiatry, University of Connecticut Health Center, Farmington 06030-2103, USA.

OBJECTIVES: A hierarchical cluster analysis was conducted using a sample of 138 school-age children with autism. The objective was to examine (1) the characteristics of resulting subgroups, (2) the relationship of these subgroups to subgroups of the same children determined at preschool age, and (3) preschool variables that best predicted school-age functioning. **METHOD:** Ninety-five cases were analyzed. **RESULTS:** Findings support the presence of 2 subgroups marked by different levels of social, language, and nonverbal ability, with the higher group showing essentially normal cognitive and behavioral scores. The relationship of high- and low-functioning subgroup membership to levels of functioning at preschool age was highly significant. **CONCLUSIONS:**

School-age functioning was strongly predicted by preschool cognitive functioning but was not strongly predicted by preschool social abnormality or severity of autistic symptoms. The differential outcome of the 2 groups shows that high IQ is necessary but not sufficient for optimal outcome in the presence of severe language impairment.

7.140. Hou, C., Miller, B.L., Cummings, J.L., Goldberg, M., Mychack, P., Bottino, V., Benson, D.F. "Artistic savants." *Neuropsychiatry Neuropsychol Behav Neurol* 2000 Jan;13(1):29-38.

Department of Neurology, Washington University, St. Louis, Missouri, USA.

OBJECTIVE: The objectives of this study were to examine common patterns in the lives and artwork of five artistic savants previously described and to report on the clinical, neuropsychological, and neuroimaging findings from one newly diagnosed artistic savant. **BACKGROUND:** The artistic savant syndrome has been recognized for centuries, although its neuroanatomic basis remains a mystery. **METHODS:** The cardinal features, strengths, and weaknesses of the work of these six savants were analyzed and compared with those of children with autism in whom artistic talent was absent. An anatomic substrate for these behaviors was considered in the context of newly emerging theories related to paradoxical functional facilitation, visual thinking, and multiple intelligences. **RESULTS:** The artists had features of "pervasive developmental disorder," including impairment in social interaction and communication as well as restricted repetitive and stereotyped patterns of behavior, interest, and activities. All six demonstrated a strong preference for a single art medium and showed a restricted variation in artistic themes. None understood art theory. Some autistic features contributed to their success, including attention to visual detail, a tendency toward ritualistic compulsive repetition, the ability to focus on one topic at the expense of other interests, and intact memory and visuospatial skills. **CONCLUSIONS:** The artistic savant syndrome remains rare and mysterious in origin. Savants exhibit extraordinary visual talents along with profound linguistic and social impairment. The intense focus on and ability to remember visual detail contributes to the artistic product of the savant. The anatomic substrate for the savant syndrome may involve loss of function in the left temporal lobe with enhanced function of the posterior neocortex.

7.141. Gomberoff, M., De Gomberoff, L.P. "Autistic devices in small children in mourning." *Int J Psychoanal* 2000 Oct;81 (Pt 5):907-20.

The authors set out to show what happens to two small girl-patients who, starting from similar events (mother's pregnancy and birth of a sibling), developed traumatic mourning that could not be managed in the way that is usual for normal or neurotic children. Autistic devices were generated in these patients in order to protect their mental economy. They consider that this way of reacting is not justified either by the quality or by the intensity of the external

stimuli and that these patients may have had a predisposition. To operate with this mechanism, the patients had to distort their mental apparatus and their own self in such a way that expressions such as language were affected in both of them: verbal language disappeared in one of them and in the other fulfilled functions other than communication. Atrophies and breaks in development to impede perception and meaning of the facts from becoming loose were also generated, strengthening the denial. The analyst's protective inclusion and his sustained effort to understand what was happening, to maintain communication and a receptive and understanding attitude, plus interpretation, made it possible for both patients to rely on a new device, constituted by the analyst, who helped to lessen the hard protective layer and make sense organs and self more permeable, processing the conflict so that more normal development could resume.

7.142. Armstrong, D., Matt, M. "Autoextraction in an autistic dental patient: a case report." *Spec Care Dentist* 1999 Mar-Apr;19(2):72-4. Publication Types: Review, Review, Tutorial.

University of Texas Health Science Center, Houston Dental Branch, General Practice Residency Program, 6516 John Freeman Avenue, Houston, TX 77030, USA.

This is a case report of a 21-year-old male patient with autism who sought treatment at a General Practice Residency clinic for dental treatment following the autoextraction of several teeth. A review of autism and self-mutilation is presented.

7.143. Liu, W., Gu, N., Feng, G., Li, S., Bai, S., Zhang, J., Shen, T., Xue, H., Breen, G., St Clair, D., He, L. "Tentative association of the serotonin transporter with schizophrenia and unipolar depression but not with bipolar disorder in Han Chinese." *Pharmacogenetics* 1999 Aug;9(4):491-5.

Shanghai Institute of Physiology, Chinese Academy of Sciences, People's Republic of China.

The serotonin transporter gene (SERT) plays an important role in the serotonin uptake into neurons. Recently, several polymorphisms including a variable-number-tandem-repeat (VNTR) in the second intron and an insertion/deletion polymorphism (5-HTT linked polymorphic region, 5-HTTLPR) were identified and reported to be associated with a variety of mental illnesses, including major depression, bipolar disorder, anxiety-related traits, and autism. In our study, we performed an association study between the SERT VNTR polymorphism and schizophrenia ($n = 260$), bipolar disorder ($n = 137$), and unipolar depression ($n = 33$) in the Han Chinese. A large group of ethnically matched control individuals ($n = 362$) were also genotyped. Allele 12 of the VNTR polymorphism was associated with schizophrenia ($P = 0.007$) and unipolar depression ($P = 0.011$). Bipolar disorder was not associated with the VNTR ($P = 0.93$). Thus, we conclude that the SERT VNTR polymorphism may be a risk factor for both schizophrenia and unipolar depression, but not for bipolar disorder, in the Han Chinese.

7.144. Dickenson, D., Shah, A. "The Bournemouth judgment: a way forward?" *Med Sci Law* 1999 Oct;39(4):280-4.

Imperial College School of Medicine, London.

In this article we provide a commentary on the various reasonings behind the Law Lords' unanimous judgements in their recent decision (25 June 1998) in *Regina v. Bournemouth Community and Mental Health NHS Trust, Ex parte L*. After summarizing the judgment and commenting on its important implications, we suggest a way forward. The 1995 Law Commission incapacity proposals, on which the 1997 consultation paper *Who Decides?* was based, do afford a mechanism which could resolve much of the practical difficulty which practitioners feared from the Appeal Court decision, whilst at the same time affording the sorts of rights which the House of Lords decision denies.

7.145. Frith, C.D., Frith, U. "Interacting minds—a biological basis." *Science* 1999 Nov 26;286(5445):1692-5. Publication Types: Review, Review, Tutorial.

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The ability to "mentalize," that is to understand and manipulate other people's behavior in terms of their mental states, is a major ingredient in successful social interactions. A rudimentary form of this ability may be seen in great apes, but in humans it is developed to a high level. Specific impairments of mentalizing in both developmental and acquired disorders suggest that this ability depends on a dedicated and circumscribed brain system. Functional imaging studies implicate medial prefrontal cortex and posterior superior temporal sulcus (STS) as components of this system. Clues to the specific function of these components in mentalizing come from single cell recording studies: STS is concerned with representing the actions of others through the detection of biological motion; medial prefrontal regions are concerned with explicit representation of states of the self. These observations suggest that the ability to mentalize has evolved from a system for representing actions.

7.146. Hermelin, B., Pring, L., Buhler, M., Wolff, S., Heaton, P. "A visually impaired savant artist: interacting perceptual and memory representations." *J Child Psychol Psychiatry* 1999 Oct;40(7):1129-39.

Psychology Department, Goldsmiths' College, University of London, UK.

In this single case study, paintings by a visually impaired and cognitively handicapped savant artist are evaluated. He paints his pictures exclusively from memory, either after having looked at a natural scene through binoculars, or after studying landscape photographs in brochures, catalogues, and books. The paintings are compared with the models from which they were derived, and the resulting generative changes are accounted for by an interaction between impaired visual input and memory transformations.

7.147. Folstein, S.E., Santangelo, S.L., Gilman, S.E., Piven, J., Landa, R., Lainhart, J., Hein, J., Wzorek, M. "Predictors of cognitive test patterns in autism families." *J Child Psychol Psychiatry* 1999 Oct;40(7):1117-28.

New England Medical Center/Tufts University School of Medicine, Boston and Eunice Kennedy Shriver Center for Developmental Disorders, Waltham, USA. susan.folstein@es.nemc.org

In a case-control study of cognitive performance, tests of intelligence, reading, spelling, and pragmatic language were administered to the parents and siblings of 90 community-ascertained probands with autism (AU group) and to the parents and siblings of 40 similarly ascertained probands with trisomy 21 Down syndrome (DS group). The two samples were comparable for age and parents' education; both groups were well-educated and had above-average intelligence. AU parents scored slightly but significantly lower on the WAIS-R Full Scale and Performance IQ, on two subtests (Picture Arrangement and Picture Completion), and on the Word Attack Test (reading nonsense words) from the Woodcock-Johnson battery. There were no differences between AU and DS siblings. As in earlier studies, AU parents, more often than DS parents, reported a history of early language-related cognitive difficulties; we were not able to replicate this in siblings. AU parents who reported such difficulties scored significantly lower on Verbal IQ, spelling, and the nonsense reading test. AU parents without a history of early language-related cognitive difficulties often had a Verbal IQ that exceeded Performance IQ by more than one standard deviation. AU siblings with early language-related difficulties had similar findings: lower Verbal IQ, poorer spelling, and poorer reading scores, compared to AU siblings without such a history. Parents with a positive history also scored worse on a measure of pragmatic language, the Pragmatic Rating Scale, but not on measures of social-related components of the broader autism phenotype. We propose that cognitive differences in a subset of autism family members are manifestations of the language-related component of the broader autism phenotype, and separate from the social-related component. This is consistent with the hypothesis that there are several genes that may interact to cause autism which segregate independently and have distinguishable manifestations in family members. The hypothesis would be further supported by finding different patterns of genetic loci linked to autism in families where one or both parents has language difficulties.

7.148. Gelisse, P., Samuelian, J.C., Genton, P. "Is schizophrenia a risk factor for epilepsy or acute symptomatic seizures?" *Epilepsia* 1999 Nov;40(11):1566-71.

Centre Saint Paul, and Service de Psychiatrie, CHU Timone, Marseille, France.

PURPOSE: The precise prevalence of epilepsies and seizures in patients with schizophrenia remains unclear. METHODS: To assess the prevalence of epilepsy and of acute symptomatic seizures in schizophrenics, we conducted a survey in an urban sector of Marseilles that includes 56,910 inhabitants, among whom 1,154 had been treated for psychiatric disorders, including 460 for schizophrenia or paranoid disorder (PD) (DSM III-R 295 and 297.1, respectively; mean age, 41.9 years; range, 17-79 years; 215 men and 245 women). RESULTS: All

460 patients were receiving long-term neuroleptic drug therapy, and 397 had been hospitalized at least once in the past year, whereas 63 were followed up as outpatients only. Seizures were present in the history of 12 patients: five had various forms of chronic epilepsy (four men, one woman; DSM III-R 295.1, one case; 295.3, two cases; 295.9, two cases), and three of these experienced seizures only after the onset of their psychiatric condition; five had acute symptomatic seizures (four men, one woman; 295.1, two cases; 295.3, 295.9, and 297.1, one case), and two had only pseudoepileptic events (both 295.3). **CONCLUSIONS:** This survey shows that the prevalence of epilepsy and acute symptomatic seizures is comparatively low in patients with schizophrenia or PD (10.8 per thousand each, respectively), and that the prevalence of a history of seizures (21.7 per thousand in this study) is not particularly increased in this middle-aged population. In contrast to childhood-onset autistic disorders, schizophrenia or PD are not major risk factors for epilepsy or acute symptomatic epileptic seizures.

7.149. Margolis, R.L., McInnis, M.G., Rosenblatt, A., Ross, C.A. "Trinucleotide repeat expansion and neuropsychiatric disease." *Arch Gen Psychiatry* 1999 Nov;56(11):1019-31. Publication Types: Review, Review, Tutorial.

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Trinucleotide, or triplet, repeats consist of 3 nucleotides consecutively repeated (e.g., CCG CCG CCG CCG CCG) within a region of DNA, a not uncommon motif in the genome of humans and other species. In 1991, a new type of genetic mutation was discovered, known as a dynamic or expansion mutation, in which the number of triplets in a repeat increases and the length becomes unstable. During the past decade, nearly 20 diseases-including Huntington disease, 2 forms of the fragile X syndrome, and myotonic dystrophy-caused by trinucleotide repeat expansions have been identified. The unstable nature of the expanded repeat leads to remarkable patterns of inheritance in these diseases, distinctly at odds with traditional notions of mendelian genetics. We review the clinical and genetic features of these disorders, with a particular emphasis on their psychiatric manifestations. We also critically examine the hypothesis that expansion mutations may have an etiologic role in psychiatric diseases such as bipolar disorder, schizophrenia, and autism.

7.150. Nilsson, F.W., Gillberg, C., Gillberg, I.C., Rastam, M. "Ten-year follow-up of adolescent-onset anorexia nervosa: personality disorders." *J Am Acad Child Adolesc Psychiatry* 1999 Nov;38(11):1389-95.

Department of Child and Adolescent Psychiatry, Annedals Clinics, Goteborg University, Sweden. ewn@medfak.gu.se

OBJECTIVE: To study the development of personality disorders, especially those involving obsessions, compulsions, and social interaction problems, in a representative group of anorexia nervosa (AN) cases. **METHOD:** The prevalence of personality disorders, obsessive-compulsive disorder, and autism spectrum disorders at mean age 24 years (10 years

after reported onset) was examined in 51 adolescent-onset AN cases recruited after community screening and 51 comparison cases matched for age, sex, and school. All 102 cases had originally been examined at age 16 years and followed up at 21 years. At 24 years, structured and validated psychiatric diagnostic interviews were performed by a psychiatrist who was blind to original diagnosis. The majority of AN cases (94%) were weight-restored. **RESULTS:** Personality disorders, particularly cluster C, and autism spectrum disorders were overrepresented in the AN group. Obsessive-compulsive personality disorder and/or autism spectrum disorder was diagnosed in a subgroup of AN cases in all 3 studies. This subgroup had a very poor psychosocial outcome. **CONCLUSIONS:** Persistent problems with obsessions, compulsions, and social interaction characterized a substantial minority of weight-restored AN cases at 10-year follow-up. These problems appear to be constitutional rather than a result of AN, and they may warrant a different treatment approach.

7.151. Ronder, R.W., Kastner, T., Parker, S.J., Walsh, K. "Serving people with developmental disabilities in Medicaid managed care." *Manag Care Q* 1999 Spring;7(2):23-30.

Columbus Medical Services, LLC, King of Prussia, PA, USA.

Concurrent with the sweeping changes in health care during the past decade, particularly in Medicaid financed health care, has been the reshaping of social policy toward people with developmental disabilities. The extent to which managed care entities match the themes now driving social services for people with mental retardation and other developmental disabilities (cerebral palsy, autism, etc.) is the extent to which they will be successful in serving this unique group of consumers of managed health care. The authors suggest a number of considerations for managed care organizations that increasingly serve significant numbers of this population.

7.152. Crino, P.B., Henske, E.P. "New developments in the neurobiology of the tuberous sclerosis complex." *Neurology* 1999 Oct 22;53(7):1384-90. Publication Types: Review, Review, Tutorial.

Department of Neurology, University of Pennsylvania Medical Center, Philadelphia 19104, USA.

OBJECTIVE: To outline recent developments in the neurobiology of the tuberous sclerosis complex (TSC). **BACKGROUND:** TSC may be associated with neuropsychiatric disorders including epilepsy, mental retardation, and autism. The uncontrolled growth of subependymal giant cell astrocytomas may lead to hydrocephalus and death. The recent identification of mutations in two genes (TSC1 and TSC2) that cause TSC has led to rapid progress in understanding the molecular and cellular pathogenesis of this disorder. How distinct mutations lead to the varied clinical phenotype of TSC is under intense investigation. **RESULTS:** We report the recent diagnostic criteria for TSC and provide an overview of the molecular genetics, molecular pathophysiology, and neuropathology of

TSC. Important diagnostic criteria for TSC include facial angiofibromas, unguinal fibromas, retinal hamartomas, and cortical tubers. Both familial and sporadic TSC cases occur. Approximately 50% of TSC families show genetic linkage to TSC1 and 50% to TSC2. Among sporadic TSC cases, mutations in TSC2 are more frequent and often accompanied by more severe neurologic deficits. Multiple mutational subtypes have been identified in the TSC1 and TSC2 genes. The TSC1 (chromosome 9) and TSC2 (chromosome 16) genes encode distinct proteins, hamartin and tuberin, respectively, which are widely expressed in the brain and may interact as part of a cascade pathway that modulates cellular differentiation, tumor suppression, and intracellular signaling. Tuberin has a GTPase activating protein-related domain that may contribute to a role in cell cycle passage and intracellular vesicular trafficking. **CONCLUSION:** Identification of tuberous sclerosis complex (TSC) gene mutations has fostered understanding of how brain lesions in TSC are formed. Further characterization of the roles of hamartin and tuberin will provide potential therapeutic avenues to treat seizures, mental retardation, and tumor growth in TSC.

7.153. Granana, N., Tuchman, R.F. "A child with severe head banging." *Semin Pediatr Neurol* 1999 Sep;6(3):221-4.

Miami Children's Hospital, Dan Marino Center, Weston, FL 33331, USA.

We present a 7-year-old boy with a developmental disorder presenting with severe head banging. Clinical evolution was consistent with diagnosis of autistic spectrum disorder, obsessive compulsive disorder, stuttering, and Tourette's syndrome. This report emphasizes the overlap between developmental disorder phenotypes. There is a need to understand the natural history and relationship of specific symptoms that occur in developmental disorders to devise effective and appropriate intervention strategies.

7.154. Hornig, M., Weissenbock, H., Horscroft, N., Lipkin, W.I. "An infection-based model of neurodevelopmental damage." *Proc Natl Acad Sci U S A* 1999 Oct 12;96(21):12102-7.

Emerging Diseases Laboratory, Department of Microbiology, University of California, Irvine, CA 92697-4292, USA.

Perinatal exposure to infectious agents and toxins is linked to the pathogenesis of neuropsychiatric disorders, but the mechanisms by which environmental triggers interact with developing immune and neural elements to create neurodevelopmental disturbances are poorly understood. We describe a model for investigating disorders of central nervous system development based on neonatal rat infection with Borna disease virus, a neurotropic noncytolytic RNA virus. Infection results in abnormal righting reflexes, hyperactivity, inhibition of open-field exploration, and stereotypic behaviors. Architecture is markedly disrupted in hippocampus and cerebellum, with reduction in granule and Purkinje cell numbers. Neurons are lost predominantly by apoptosis, as supported by increased mRNA levels for pro-apoptotic products (Fas, caspase-1), decreased mRNA levels for the

anti-apoptotic bcl-x, and in situ labeling of fragmented DNA. Although inflammatory infiltrates are observed transiently in frontal cortex, glial activation (microgliosis > astrocytosis) is prominent throughout the brain and persists for several weeks in concert with increased levels of proinflammatory cytokine mRNAs (interleukins 1alpha, 1beta, and 6 and tumor necrosis factor alpha) and progressive hippocampal and cerebellar damage. The resemblance of these functional and neuropathologic abnormalities to human neurodevelopmental disorders suggests the utility of this model for defining cellular, biochemical, histologic, and functional outcomes of interactions of environmental influences with the developing central nervous system.

7.155. Russell, J., Saltmarsh, R., Hill, E. "What do executive factors contribute to the failure on false belief tasks by children with autism?" *J Child Psychol Psychiatry* 1999 Sep;40(6):859-68.

Department of Experimental Psychology, Cambridge University, UK.

As children with autism have pervasive executive difficulties it is necessary to determine whether these contribute to their often-reported failure on the false belief task. Failure on this task is frequently taken to diagnose the lack of a "theory of mind". We report two studies using two tasks that make similar executive demands to the false belief task. The first experiment showed that children with autism are significantly challenged by a "conflicting desire" task, which suggests that their difficulty with the false belief task is not rooted in difficulty with grasping the representational nature of belief. In the second study children with autism were also found to be impaired on a novel version of the "false photograph task". A parsimonious reading of these data is that their difficulty with all three tasks is due to commonalities in the tasks' executive structure.

7.156. Saugstad, L.F. "A lack of cerebral lateralization in schizophrenia is within the normal variation in brain maturation but indicates late, slow maturation." *Schizophr Res* 1999 Oct 19;39(3):183-96. Publication Types: Review, Review Literature.

Department of Anatomy, Institute of Basic Medical Sciences, University of Oslo, Norway.

The planum temporale (PT) bias, PT leftward, PT symmetry, and PT rightward reversal and sidedness preference, consistent right-handedness, ambilaterality, and consistent left-handedness are placed on a continuum mirroring the normal variation in rate of brain maturation. Maturation rate declines as we pass from PT leftward bias and consistent right-handedness to PT reversal and consistent left-handedness. Concomitantly, we expect an increased prevalence of males due to their pubertal age being about 2 years later than that of females, and a shift in cognitive profile from higher verbal scores than performance scores on the WAIS to higher performance than verbal scores. Three disorders fulfilling the criteria of late CNS maturation apart from the corresponding cognitive profile were studied: infantile autism (IA),

schizophrenia (S), and developmental dyslexia (DD). These disorders have in common deficits in cognition, perception, and somatomotor function. The deficits range from an arrest in brain development (which is evident in infancy superimposed on late maturation in IA) to overall delayed brain and somatic development in S (culminating in postpubertal psychotic episodes and persistent and generalized residual deficits). Finally, reading inability, problems in perception (vision and hearing) and in motor coordination, particularly between the two hemispheres, characterize DD. Enhancing brain maturation and the prevalence of 'normal' cerebral asymmetry—laterality is preferable if we want to reduce the risk of developing the above-mentioned disorders. It is suggested that in the past environmental challenges have favored early maturation, with its abundant neuronal population, arborization and excessive density of synapses and cerebral excitability which has powered evolution through the mechanism of natural selection. Early maturation is obtainable through optimal nutrition, including a satisfactory amount of marine fat (PUFA), before and during pregnancy and later in life.

7.157. El Abd, S., Patton, M.A., Turk, J., Hoey, H., Howlin, P. "Social, communicational, and behavioral deficits associated with ring X turner syndrome." *Am J Med Genet* 1999 Oct 15;88(5):510-6.

Child and Adolescent Psychiatry, St. George's Hospital Medical School, London, United Kingdom. selabd@sghms.ac.uk

We describe the cognitive and behavioral characteristics of five individuals with a ring X chromosome. All subjects had a small active (early replicating) ring X chromosome. The X inactive specific transcript (XIST) locus was confirmed by fluorescent in situ hybridisation (FISH) to be present in all ring X chromosomes. Mental retardation was present in four individuals. All patients with or without mental retardation had a characteristic profile of aggression toward self and others, episodes of screaming, attentional problems, and impulsiveness. Autistic-like features were also present in all individuals and included limited communication, obsessive compulsive behavior, and social difficulties. In some cases the obsessive behavior was extreme and incapacitating. This characteristic behavioral profile may aid the diagnosis and future understanding of ring X.

7.158. Hong, K.E., Kim, J.H., Moon, S.Y., Oh, S.K. "Chromosomal abnormalities in child psychiatric patients." *J Korean Med Sci* 1999 Aug;14(4):377-85.

Department of Child and Adolescent Psychiatry, College of Medicine, Seoul National University, Korea. kehong@plaza.snu.ac.kr

To determine the frequency of chromosomal abnormalities in a child psychiatric population, and to evaluate possible associations between types of abnormalities and patient's clinical characteristics, cytogenetic examination was performed on 604 patients. Demographic data, reasons for karyotyping, clinical signs, and other patient characteristics

were assessed and correlated with the results from karyotyping. Chromosomal abnormalities were found in 69 patients (11.3%); these were structural in 49 cases and numerical in 20. Inversion of chromosome nine was found in 15 subjects, trisomy of chromosome 21 in 11, and fragile X in five patients. When karyotyping was performed because of intellectual impairment or multiple developmental delay, significantly more abnormalities were found than average; when performed because autistic disorder was suspected, the number of abnormalities was significantly fewer. There were no differences in clinical variables between structural and numerical abnormalities, nor among nine types of chromosomal abnormalities, except that numerical abnormalities and polymorphism were found at a later age, and that walking was more delayed and IQ was lower in patients with Down syndrome. Clinicians should be aware of the possible presence of chromosomal abnormalities in child psychiatric populations; the close collaboration with geneticists and the use of more defined guidelines for cytogenetic investigation are important.

7.159. Miller, M.T., Stromland, K. "The mobius sequence: a relook." *J AAPOS* 1999 Aug;3(4):199-208.

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BACKGROUND: The constellations of findings often referred to as Mobius syndrome might be better described as Mobius sequence, because the term sequence defines a cascade of secondary events after an embryonic insult from heterogeneous causes. Classic clinical findings include evidence of sixth and seventh cranial nerve involvement, often with associated malformations of limbs, craniofacial structures, and other cranial nerves. **METHODS:** A prospective study was undertaken in Sweden of 25 patients who showed characteristic findings of Mobius sequence. **RESULTS:** Of the patients who did not have strabismus surgery, 10 patients had straight eyes in the primary position, 7 had esotropia, 2 had exotropia, and 1 had hypertropia. All had significant limitation of abduction, except 1 patient with exotropia who showed minimal underaction on abduction but a large limitation of adduction. In the description in these early cases, some patients manifested a clinical pattern resembling a horizontal gaze paresis. Narrowing of the palpebral fissure on adduction similar to that seen in Duane syndrome was observed in a few cases. Two patients had ptosis. Nineteen patients had diminished facial expression bilaterally, often asymmetric, and 6 cases appeared to be unilateral. Seven patients had abnormal tearing. Associated systemic findings included Poland anomaly (2), club feet or other limb anomalies (8), micrognathia (8), tongue malformations (17), cleft palate (5), and speech problems (18). An unusual finding was autism syndrome (6) or autism-like syndrome (1). **CONCLUSIONS:** The associated findings in Mobius sequence may give further clues to the location and timing of the developmental disturbance. The wide range of ocular motility patterns suggests that the previous concept of a lesion solely in the sixth nerve nucleus is an inadequate explanation for these findings.

7.160. York, A., von Fraunhofer, N., Turk, J., Sedgwick, P. "Fragile-X syndrome, Down's syndrome and autism: awareness and knowledge amongst special educators." *J Intellect Disabil Res* 1999 Aug;43 (Pt 4):314-24.

Department of General Psychiatry, Jenner Wing, St George's Hospital Medical School, London, UK.

Fragile-X syndrome is the commonest cause of inherited intellectual disability. There is good evidence for a behavioural phenotype. This has implications for school staff using standard educational techniques. Similarly, autism is known to create particular educational requirements. The present study examined the awareness and knowledge of fragile-X syndrome, Down's syndrome and autism amongst staff in special and mainstream education. One hundred and two special school staff and 40 mainstream school staff completed questionnaires. Most staff offered a variety of features 'typical' of Down's syndrome and autism. In contrast, staff knew less about fragile-X syndrome. Specific knowledge about the learning styles of these children was very poor, but was associated with having taught an affected child. Mainstream and special school staff offered similar levels of knowledge for all three conditions. Staff did not demonstrate a sufficiently specialized knowledge of fragile-X syndrome to ensure that the special educational needs of these children were being met fully.

7.161. Bara, B.G., Bosco, F.M., Bucciarelli, M. "Developmental pragmatics in normal and abnormal children." *Brain Lang* 1999 Jul;68(3):507-28. Publication Types: Review, Review, Tutorial.

Centro di Scienza Cognitiva, Universita di Torino, Torino, Italy.

We propose a critical review of current theories of developmental pragmatics. The underlying assumption is that such a theory ought to account for both normal and abnormal development. From a clinical point of view, we are concerned with the effects of brain damage on the emergence of pragmatic competence. In particular, the paper deals with direct speech acts, indirect speech acts, irony, and deceit in children with head injury, closed head injury, hydrocephalus, focal brain damage, and autism. Since no single theory covers systematically the emergence of pragmatic capacity in normal children, it is not surprising that we have not found a systematic account of deficits in the communicative performance of brain injured children. In our view, the challenge for a pragmatic theory is the determination of the normal developmental pattern within which different pragmatic phenomena may find a precise role. Such a framework of normal behavior would then permit the systematic study of abnormal pragmatic development. Copyright 1999 Academic Press.

7.162. Agulhon, C., Abitbol, M., Bertrand, D., Malafosse, A. "Localization of mRNA for CHRNA7 in human fetal brain." *Neuroreport* 1999 Aug 2;10(11):2223-7.

Departement de Psychiatrie, Hopitaux Universitaires de Geneve (HUG), Chene-Bourg, Switzerland.

The aim of this study was to determine the regional distribution in situ of the mRNA for the alpha 7 subunit of the neuronal nicotinic acetylcholine receptor in human fetal brain. We found high levels of alpha 7 gene expression in nuclei that receive sensory information, such as those of the neocortex and hippocampus, the thalamic nuclei, the reticular thalamic nucleus, the pontine nuclei and the superior olive complex. These data support a possible regulatory function for alpha 7-containing receptors in sensory processing, which may be involved in the pathological physiology of schizophrenia and autism. Early alpha 7 gene expression is also consistent with a morphogenetic role for alpha 7 receptors in central nervous system development.

7.163. Ritvo, R.Z., Papilsky, S.B. "Effectiveness of psychotherapy." *Curr Opin Pediatr* 1999 Aug;11(4):323-7. Publication Types: Review, Review, Tutorial.

Committee on Psychotherapy, American Academy of Child and Adolescent Psychiatry, New York, USA.

Meta-analytic studies demonstrate that psychotherapy works. This paper reviews the methodologic challenges that slow the research needed to explain what works, how, and for whom. The definition of psychotherapy is addressed briefly. Recognizing both the accomplishments and limitations of the recent focus on efficacy studies of highly specified therapies, researchers are turning to examining the effectiveness of psychotherapies. Effectiveness research examines issues of feasibility, ease in generalizing, and costs versus benefits. Research designers are interested in both moderators and mediators of treatment effect. Developmental theory and developmental psychopathology provide valuable focuses for research design. The paucity of research on process, on psychodynamic psychotherapies, and on combined treatments is noted. The paper concludes with a summary of recent psychotherapy research in several specific categories: prevention, autism, anxiety disorders, disruptive disorders, and depression.

7.164. Ho, P.K., Fong, R.S., Kai, H.S., Lau, E.H., Ngan, E.S., Cotton, C.U., Chow, B.K. "The human secretin receptor gene: genomic organization and promoter characterization." *FEBS Lett* 1999 Jul 23;455(3):209-14.

Department of Zoology, The University of Hong Kong, SAR, PR China.

Secretin is the most potent regulator of pancreatic bicarbonate, electrolyte and volume secretion. In this report, the organization of the human secretin receptor (hSR) gene was characterized by overlapping genomic phage clones. The hSR gene consists of 13 exons and 12 introns with all the splice donor and acceptor sites conforming to the canonical GT/AG rule. By transient reporter gene assays, the wild-type promoter, containing 3.0 kb of the hSR gene 5' flanking region, was able to drive 5.8 +/- 0.6 and 6.6 +/- 0.2-fold ($P < 0.01$) increases in luciferase activities in pancreatic ductule-derived PANC-1 and BPD-1 cells, respectively. By subsequent 5' and 3' deletion analysis, a promoter element was identified within

-408 to -158, relative to the ATG codon. This promoter element was found to be cell-specific since it could drive reporter gene expression in PANC-1 and BPD-1 cells but not in Hs 262.St, Hs 746T and alphaT3-1 cells. The study of the transcriptional control of human secretin and its receptor should shed light on the pathological developments of pancreatic cancer and autism in the future.

7.165. Telvi, L., Lebbar, A., Del Pino, O., Barbet, J.P., Chaussain, J.L. "45,X/46,XY mosaicism: report of 27 cases." *Pediatrics* 1999 Aug;104(2 Pt 1):304-8.

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OBJECTIVES: There exist substantial differences between prenatally and postnatally diagnosed cases of 45,X/46,XY mosaicism. Ninety percent of prenatally diagnosed cases show a normal male phenotype, whereas the postnatally diagnosed cases show a wide spectrum of phenotypes. This 10% risk of an abnormal outcome in prenatally diagnosed cases requires further attention. The purpose of the present study is to provide more information on the postnatally diagnosed 45,X/46,XY mosaicism cases. To date, only a few series have been reported. An accurate diagnosis in these patients is essential not only to their follow-up, but also to providing appropriate genetic counselling and subsequent prenatal diagnosis to their parents. **METHODS:** The clinical, cytogenetic, endocrinologic, histologic and molecular biological findings of 27 patients with 45, X/46,XY mosaicism are analyzed. **RESULTS:** The reported cases showed a wide spectrum of phenotypes as Turner syndrome, mixed gonadal dysgenesis (MGD), male pseudohermaphroditism (MPH) and apparently normal male. However, Ulrich-Turner stigmata were the most common features found in this series. Patients with MGD or MPH presented with various degrees of sex reversal such as hypospadias and/or abnormal internal genitalia. No correlation between the proportion of the 45,X/46,XY cell lines in the blood or the fibroblasts and the phenotype was found. Mild mental retardation was present in 4 of the patients and 2 patients showed signs of autism. **CONCLUSIONS:** Two major points are emphasized in this series: 1) the presence in 7 histologically analyzed streak gonads of a homogeneous 45,X chromosomal complement suggests that the invasion of the primitive genital ridge by a such a cell line may induce abnormal gonadal development; 2) 3 males, apparently normal at birth, developed late onset abnormalities such as dysgenetic testes leading to infertility, Ulrich-Turner stigmata, dysmorphic features, and mild mental retardation. These data indicate the importance of an accurate clinical and histologic evaluation of any patient presenting with 45, X/46,XY mosaicism.

7.166. Matson, J.L., Rush, K.S., Hamilton, M., Anderson, S.J., Bamburg, J.W., Baglio, C.S., Williams, D., Kirkpatrick-Sanchez, S. "Characteristics of depression as assessed by the Diagnostic Assessment for the Severely Handicapped-II (DASH-II)." *Res Dev Disabil* 1999 Jul-Aug;20(4):305-13.

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Fifty-seven individuals with severe and profound mental retardation (18 with a DSM-IV diagnosis of depression, 19 with a Diagnostic Statistical Manual, 4th edition diagnosis of autism, and 20 who meet no criteria for an emotional disorder) were studied. The validity of the Diagnostic Assessment for the Severely Handicapped II depression subscale was evaluated to determine its value in categorizing individuals in these two groups. Suggestions were made for diagnosing depression in persons with severe and profound mental retardation. In a second study the above individuals were compared on symptomology to assess comorbidity with related symptoms. These "core," peripheral, or associated features of depression were identified. Implications of the findings for describing and defining depression in these persons are discussed.

7.167. Mervis, C.B., Robinson, B.F. "Methodological issues in cross-syndrome comparisons: matching procedures, sensitivity (Se), and specificity (Sp)" *Monogr Soc Res Child Dev* 1999;64(1):115-30; discussion 131-9. Publication Types: Comment.

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We are impressed with the magnitude and potential importance of the studies presented by Sigman and Ruskin in this monograph. The within-syndrome findings for the children with autism concerning relations between early joint attention and a range of cognitive abilities a full 9 years later provide the strongest evidence so far that early nonverbal communication skills play an important role in the later development of language, intelligence, and social relations with peers. The purpose of the monograph was not limited to within-syndrome research questions, however. Sigman and Ruskin state that a major goal of the research reported in the monograph was to identify specific, unique, and universal deficits for autism and Down syndrome. They base their method of identifying such syndrome characteristics on the group-matching procedure. Given that this procedure is fraught with difficulties, we are concerned that many of Sigman and Ruskin's cross-syndrome comparisons may be incorrect. We do not mean to single out Sigman and Ruskin. The group-matching method is frequently used in special populations research, with the null hypothesis of no differences on the control variable being accepted at dangerously low p values. Our concerns with the group-matching problem extend to much of the extant research that attempts to identify characteristics of individuals based on the performance of their syndrome group relative to a control group. The profiling procedure we outlined seems more fruitful and conceptually satisfying than the traditional matching method. When profiling is not possible, however, it is important to consider the impact of CA confounds and statistical decision procedures used to ensure matching on the control variable, when interpreting syndrome differences on variables of interest.

7.168. Happe, F., Brownell, H., Winner, E. "Acquired 'theory of mind' impairments following stroke." *Cognition* 1999 Apr 1;70(3):211-40. Publication Types: Clinical Trial, Controlled Clinical Trial.

Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK.

The ability to attribute thoughts and feelings to self and others ('theory of mind') has been hypothesised to have an innate neural basis and a dedicated cognitive mechanism. Evidence in favour of this proposal has come from autism; a brain-based developmental disorder which appears to be characterised by impaired theory of mind, despite sometimes good general reasoning skills/IQ. To date no case of specific acquired theory of mind impairment has been reported. The present study examined theory of mind in adults who had suffered right hemisphere stroke, a group known to show pragmatic and social difficulties. In one study using story materials and two using cartoons, patients' understanding of materials requiring attribution of mental states (e.g. ignorance, false belief) was significantly worse than their understanding of non-mental control materials. Data from healthy elderly subjects, and a small group of left hemisphere patients (who received the tasks in modified form), suggest that this impairment on mental state tasks is not a function of task difficulty. The findings support the notion of a dedicated cognitive system for theory of mind, and suggest a role for the healthy right hemisphere in the attribution of mental states.

7.169. Townsend, J., Courchesne, E., Covington, J., Westerfield, M., Harris, N.S., Lyden, P., Lowry, T.P., Press, G.A. "Spatial attention deficits in patients with acquired or developmental cerebellar abnormality." *J Neurosci* 1999 Jul 1;19(13):5632-43.

Department of Neurosciences, University of California, San Diego, La Jolla, California 92093-0217, USA.

Recent imaging and clinical studies have challenged the concept that the functional role of the cerebellum is exclusively in the motor domain. We present evidence of slowed covert orienting of visuospatial attention in patients with developmental cerebellar abnormality (patients with autism, a disorder in which at least 90% of all postmortem cases reported to date have Purkinje neuron loss), and in patients with cerebellar damage acquired from tumor or stroke. In spatial cuing tasks, normal control subjects across a wide age range were able to orient attention within 100 msec of an attention-directing cue. Patients with cerebellar damage showed little evidence of having oriented attention after 100 msec but did show the effects of attention orienting after 800-1200 msec. These effects were demonstrated in a task in which results were independent of the motor response. In this task, smaller cerebellar vermal lobules VI-VII (from magnetic resonance imaging) were associated with greater attention-orienting deficits. Although eye movements may also be disrupted in patients with cerebellar damage, abnormal gaze shifting cannot explain the timing and nature of the attention-orienting deficits reported here. These data may be consistent

with evidence from animal models that suggest damage to the cerebellum disrupts both the spatial encoding of a location for an attentional shift and the subsequent gaze shift. These data are also consistent with a model of cerebellar function in which the cerebellum supports a broad spectrum of brain systems involved in both nonmotor and motor function.

7.170. Mouridsen, S.E., Rich, B., Isager, T. "Psychiatric morbidity in disintegrative psychosis and infantile autism: A long-term follow-up study." *Psychopathology* 1999 Jul-Aug;32(4):177-83.

Department of Child and Adolescent Psychiatry, Bispebjerg Hospital, Copenhagen, Denmark.

In order to study the validity of disintegrative psychosis (DP), the authors compared 13 patients given this diagnosis in childhood with a control group of 39 patients with infantile autism (IA) matched for sex, age, IQ and social class on measures of psychiatric morbidity. Almost the same proportion of the two groups had been admitted to a psychiatric hospital during a 22-year follow-up period. However, there was a slight tendency (statistically nonsignificant) for the DP group to utilize the psychiatric health care system more frequently than the IA group. They had more admissions and stayed longer in hospital than patients with IA suggesting that they had more psychiatric symptoms than the IA group. The original IA diagnoses were confirmed fairly consistently during the follow-up period, while the DP group was given more heterogeneous diagnoses. No diagnosis of schizophrenia was made in either group.

7.171. Bellugi, U., Lichtenberger, L., Mills, D., Galaburda, A., Korenberg, J.R. "Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome." *Trends Neurosci* 1999 May;22(5):197-207. Publication Types: Review, Review, Tutorial.

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Williams syndrome (WMS) is a rare sporadic disorder that yields a distinctive profile of medical, cognitive, neurophysiological, neuroanatomical and genetic characteristics. The cognitive hallmark of WMS is a dissociation between language and face processing (relative strengths) and spatial cognition (profound impairment). Individuals with WMS also tend to be overly social, behavior that is opposite to that seen in autism. A genetic hallmark of WMS is a deletion on chromosome band 7q11.23. Williams syndrome is also associated with specific neuromorphological and neurophysiological profiles: proportional sparing of frontal, limbic and neocerebellar structures is seen using MRI; and abnormal functional organization of the neural systems that underlie both language and face processing is revealed through studies using event-related potentials. The non-uniformity in the cognitive, neuromorphological and neurophysiological domains of WMS make it a compelling model for elucidating the relationships between cognition, the brain and, ultimately, the genes.

7.172. Halfon, N., Newacheck, P.W. "Prevalence and impact of parent-reported disabling mental health conditions among U.S. children." *J Am Acad Child Adolesc Psychiatry* 1999 May;38(5):600-.

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OBJECTIVE: To provide a current national profile of the prevalence and impact of parent-reported disabling mental health conditions in U.S. children. **METHOD:** A cross-sectional descriptive analysis of 99,513 children younger than 18 years old included in the 1992-1994 National Health Interview Survey (NHIS). The response rate exceeded 94% in each year. Disability is defined as the long-term reduction in a child's ability to perform social role activities, such as school or play, as a result of his/her mental health condition. **RESULTS:** On average, 2.1% of U.S. children were reported to suffer from a disabling mental health condition in 1992-1994. The most common reported causes of disability include mental retardation, attention-deficit hyperactivity disorder, and learning disabilities. While national prevalence estimates were produced for some low-prevalence conditions such as autism (38/100,000), for many specific diagnoses the reported prevalence rates were too low for accurate national population estimates using this data set. Logistic regression analysis demonstrates that prevalence of a disabling mental health condition was higher for older children; males; children from low-income, single-parent families; and those with less education. These conditions are also associated with high rates of special education participation (approximately 80%) and health system use. **CONCLUSIONS:** The NHIS provides a useful and untapped resource for estimating the prevalence of disabling mental health conditions. These conditions are increasingly prevalent and have a profound impact on children and the educational and health care systems.

7.173. Cipolotti, L., Robinson, G., Blair, J., Frith, U. "Fractionation of visual memory: evidence from a case with multiple neurodevelopmental impairments." *Neuropsychologia* 1999 Apr;37(4):455-65.

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It is known that the adult visual memory system is fractionable into functionally independent cognitive subsystems, selectively susceptible to brain damage. However, it is unclear whether these cognitive subsystems can fractionate developmentally. The present study describes an investigation of visual memory of a patient (PE) with multiple developmental disorders. PE was congenitally deaf, had Gilles de la Tourette syndrome and autism, with non-verbal ability in the normal range. The patient presented with a recognition memory impairment for unknown human faces. This contrasted with his superior recognition memory for unknown buildings, landscapes and outdoor scenes. PE's memory impairment for faces could not be explained by a general deficit in face processing. Interestingly, PE also showed a recognition memory impairment for animals. These findings

indicate that different domains of the visual memory system can be fractionated developmentally. In particular, it demonstrates that topographical memory can develop independently from other aspects of visual memory.

7.174. Snyder, A.W., Mitchell, D.J. "Is integer arithmetic fundamental to mental processing?: the mind's secret arithmetic." *Proc R Soc Lond B Biol Sci* 1999 Mar 22;266(1419):587-92. Publication Types: Review, Review, Tutorial.

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Unlike the ability to acquire our native language, we struggle to learn multiplication and division. It may then come as a surprise that the mental machinery for performing lightning-fast integer arithmetic calculations could be within us all even though it cannot be readily accessed, nor do we have any idea of its primary function. We are led to this provocative hypothesis by analysing the extraordinary skills of autistic savants. In our view such individuals have privileged access to lower levels of information not normally available through introspection.

7.175. Blatt, S.D., Meguid, V., Church, C.C., Botash, A.S., Jean-Louis, F., Siripornsawan, M.P., Weinberger, H.L. "Sudden infant death syndrome, child sexual abuse, and child development." *Curr Opin Pediatr* 1999 Apr;11(2):175-86. Publication Types: Review, Review, Tutorial.

State University of New York, Health Science Center at Syracuse 13210, USA.

Since the introduction of the Back to Sleep Campaigns, there has been a dramatic reduction in sudden infant death syndrome in this country. Steven Blatt and Victoria Meguid review the literature surrounding sleep position. Investigators have continued efforts to find other modifiable risk factors of sudden infant death syndrome. A prospective study of more than 33,000 neonates found a link between a prolonged QT electrocardiogram interval and sudden infant death syndrome. Also discussed are investigations seeking to explain the relationship between smoking and sudden infant death syndrome. Ann Botash, Florence Jean-Louis and Mongkae Ploy Siripornsawan review the latest thinking on genital warts and their relation to specific viral etiologies and child sexual abuse. Other symptoms and signs of sexual abuse are the focus of a number of articles that can help the practitioner care for these unfortunate children. Catherine Church reviews medication options for children diagnosed with pervasive developmental disorders or autism spectrum disorders. Finally, in this article, risperidone, fluoxetine and naltrexone are reviewed.

7.176. Kuhn, D.E., DeLeon, I.G., Fisher, W.W., Wilke, A.E. "Clarifying an ambiguous functional analysis with matched and mismatched extinction procedures." *J Appl Behav Anal* 1999 Spring;32(1):99-102.

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Results of functional analysis were ambiguous in suggesting that self-injurious behavior (SIB) was maintained by escape, sensory reinforcement, or both. To help clarify these results, we compared escape extinction, sensory extinction, and the combined treatments. Sensory extinction proved to be a necessary and sufficient treatment, whereas escape extinction failed to decrease SIB. These analyses helped to clarify the function of SIB and to identify an effective and efficient treatment.

7.177. Sigafos, J., Roberts-Pennell, D., Graves, D. "Longitudinal assessment of play and adaptive behavior in young children with developmental disabilities." *Res Dev Disabil* 1999 Mar-Apr;20(2):147-61.

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Deficits in appropriate play have been widely documented among children with developmental disabilities. However, there has been little research on the development of play or the relation between play and adaptive behavior in such children. The present study involved a longitudinal assessment of play and adaptive behavior among 13 preschool children with developmental disabilities. Children were assessed every 6 months over a 3-year period. Assessments included standardized ratings of adaptive behavior and videotape observations during unstructured free-play times in the preschool classroom. Adaptive behavior increased by almost one standard deviation from the first to the last round of data collection. Appropriate play was observed during approximately 20% of each 30-min observation and showed little overall change over 3 years of study. Observed play was primarily functional (57%) and exploratory (28%) with less constructive (5%) and pretend (10%) play. Adaptive behavior scores were not consistently correlated with the amount or type of play. The results suggest little overall relation between appropriate play and other major domains of adaptive behavior. Implications for play-based assessment and intervention in early childhood special education are discussed.

7.178. Farrant, A., Boucher, J., Blades, M. "Metamemory in children with autism." *Child Dev* 1999 Jan-Feb;70(1):107-31.

Department of Psychology, University of Warwick, UK. j.boucher@warwick.ac.uk

Five experiments are reported comparing metamemory abilities in children with autism, age- and language-matched mentally retarded children, and language-matched young normal controls. The mean language age of the participants in Experiment 1 was approximately 6 years, in Experiments 2, 3, and 4 approximately 8 years, and in Experiment 5 approximately 9 years. All the children were given one or more false belief tests. Experiment 1 assessed the children's understanding that a task variable (list length) and a person variable (age) will affect their own and others' performances on an immediate auditory-verbal recall task. Experiment 2 assessed the ability to utilize category cues in a picture recall task. Experiments 3 and 4 assessed the ability to verbalize strategies used in a memory span test and in one retrospective

and two prospective memory situations. Experiment 5 assessed the children's knowledge and understanding of another person's memory. On the basis of available evidence and theory, we predicted that the children with autism would be impaired on all the metamemory tasks and that impairment would be associated with failure on tests of false belief. Our predictions were not supported. The children with autism were not impaired on any of the metamemory tasks, although they were less likely than controls to make spontaneous use of memory strategies involving other people. Unexpectedly few of the children failed the false belief tasks. These results are discussed in relation to theories concerning primary psychological deficits underlying autism.

7.179. Ryan, S.G. "Genetic susceptibility to neurodevelopmental disorders." *J Child Neurol* 1999 Mar;14(3):187-95. Publication Types: Review, Review, Academic.

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A large body of evidence suggests that genetic factors influence liability to many common neurodevelopmental disorders. Examples include Tourette syndrome, attention-deficit hyperactivity disorder, autism, and dyslexia. Characterization of the genetic component of susceptibility to these conditions at a molecular level should improve classification, elucidate fundamental neurobiologic mechanisms of disease, and suggest novel approaches to treatment. Susceptibility loci for complex traits could be identified by detecting linkage to a well-mapped genetic marker or by detecting association with a putative high-risk allele at a candidate locus. This article reviews the principles underlying these complementary approaches, and notes recent progress in specific conditions. As the molecular epidemiology of susceptibility to common neurodevelopmental disorders emerges, it might be increasingly possible to identify "high-risk" and "low-risk" genotypes. Clinicians should understand the nature of this kind of information in order to appreciate its power as well as its limitations.

7.180. Mottron, L., Burack, J.A., Stauder, J.E., Robaey, P. "Perceptual processing among high-functioning persons with autism." *J Child Psychol Psychiatry* 1999 Feb;40(2):203-11.

Clinique Specialisee de l'Autisme et Service de recherche, Hopital Riviere-des-Prairies, and Universite de Montreal, Canada. mottron@istar.ca

Two tasks were used to assess the processing of whole versus parts of objects in a group of high-functioning children and adolescents with autism (N = 11) and a comparison group of typically developing peers (N = 11) matched for chronological age and IQ. In the first task, only the children with autism showed a global advantage, and the two groups showed similar interference between levels. In the second task, the children with autism, despite longer RTs, showed similar

performance to the comparison group with regard to the effect of goodness on visual parsing. Contrary to expectations based on the central coherence and hierarchisation deficit theories, these findings indicate intact holistic processing among persons with autism. The implications of these findings are discussed in relation to apparently discrepant evidence from other studies.

7.181. Rutter, M. "The Emanuel Miller Memorial Lecture 1998. Autism: two-way interplay between research and clinical work." *J Child Psychol Psychiatry* 1999 Feb;40(2):169-88. Publication Types: Historical Article, Lectures.

MRC Child Psychiatry Unit and Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London, UK.

The two-way interplay between research and clinical practice in relation to autism is reviewed with respect to: (1) diagnosis and syndrome delineation; (2) the nature of the disorder; (3) intervention studies; and (4) aetiology, as manifest during four time periods; (a) the 1950s and 1960s; (b) the 1970s into the mid 1980s; (c) the late 1980s and early 1990s; and (d) the late 1990s. It is concluded that clinical practice has changed out of all recognition during the last 50 years and that research findings have been crucial in bringing about that change. It has not, however, been a one-way traffic. Many key advances were prompted by astute clinical observations and some extravagant research claims were given a more balanced perspective through the light of clinical experience. Crucial research and clinical tasks remain but the means to meet them are there if the opportunities are taken and attention is paid to the lessons of the past.

7.182. Michaelovsky, E., Frisch, A., Rockah, R., Peleg, L., Magal, N., Shohat, M., Weizman, R. "A novel allele in the promoter region of the human serotonin transporter gene." *Mol Psychiatry* 1999 Jan;4(1):97-9.

Laboratory of Biochemical Genetics, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, Israel.

The human serotonin transporter (hSERT) gene is a promising candidate for mediating the genetic susceptibility for various psychiatric conditions such as mood and obsessive-compulsive disorders. Two polymorphic sites in this gene attracted much interest: a VNTR of 17-bp repeats in intron two, and an insertion/deletion in the 5'-flanking promoter region (5-HTT gene-linked polymorphic region-5-HTTLPR) creating a short (S) and a long (L) allele. The 5-HTTLPR polymorphism is situated in a GC-rich region composed of 20-23 bp repeating units. The S and L alleles have 14 and 16 repeat-elements respectively. Positive associations of the 5-HTTLPR polymorphism with mood disorders, anxiety-related personality traits, autism and late-onset Alzheimer's disease have been published, although some non replications were also reported. Here we report a novel allele (termed LJ) in the 5-HTTLPR site. This allele is longer than the L allele by 43 bp, has 18 repeat units and contains two copies of the insertion/deletion sequence arranged in tandem. The LJ allele was found in individuals of Libyan and Tunisian Jewish origin but not in Moroccan or Ashkenazi Jews.

7.183. Heavey, L., Pring, L., Hermelin, B. "A date to remember: the nature of memory in savant calendrical calculators." *Psychol Med* 1999 Jan;29(1):145-60.

Goldsmiths College, University of London.

BACKGROUND: Savant calendar calculators can supply with speed the day of the week of a given date. Although memory is suggested to be an important component of this unusual ability, memory function has never been systematically investigated in these skilled yet learning impaired individuals. **METHODS:** Eight savant calendrical calculators, most of whom had autism, were compared with eight verbal IQ, age and diagnosis matched controls on digit and word span tests and measures of long-term memory for words and calendrical information (individual years). In an analogue to the 'generation effect', the savants' memory for dates was also compared following calculation and study/read tasks. **RESULTS:** The savants did not differ from controls on measures of general short- and long-term memory. They did, however, show a clear recall superiority for the long-term retention of calendrical material. They also remembered calculated dates better than those that were only studied. **CONCLUSIONS:** A general mnemonic advantage cannot explain savant date calculation skills. Rather, through exposure to date information, the savants are suggested to develop a structured calendar-related knowledge base with the process of calculation utilizing the interrelations within this knowledge store. The cognitive processing style characteristic of autism may also play a role in the acquisition of this savant ability.

7.184. Williams, P.G., Bloom, A.S. "Case reports in autism: issues in diagnosis and treatment." *J Ky Med Assoc* 1999 Feb;97(2):56-60.

University of Louisville Child, Evaluation Center, KY 40202, USA.

Autism is a relatively common developmental disorder characterized by pervasive impairments in communication and social interaction as well as restricted interests and repetitive behaviors. Two case reports are presented to illustrate important aspects of diagnosis and treatment. Early clinical diagnosis is essential so that appropriate intervention can be implemented. A multidisciplinary approach to treatment is recommended due to the impact of autism on many aspects of behavior and development.

7.185. Fattal-Valevski, A., Kramer, U., Leitner, Y., Nevo, Y., Greenstein, Y., Harel, S. "Characterization and comparison of autistic subgroups: 10 years' experience with autistic children." *Dev Med Child Neurol* 1999 Jan;41(1):21-5.

The Institute for Child Development and Pediatric Neurology Unit, Division of Pediatrics, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Israel.

To summarize our 10-year experience with autistic children at the Tel Aviv Child Development Center, the files of all 55 children with autism treated at our center over a 10-year period were retrospectively reviewed. Particular attention was

addressed to the value of the medical work-up in detecting the etiology of autism and to factors differentiating infantile autism (IA) from autistic-like behavior (ALB). Twenty-four subjects (44%) had IA and 31 (56%) had ALB. These subgroups were compared for demographic, perinatal, familial, neurological, and psychological findings, and outcome at discharge. Associated medical conditions and the yield of metabolic work-up and neuroimaging and electroencephalography studies are discussed. The two subgroups differed only in severity of autistic symptoms and cognitive function ($P < 0.05$), but not in demographic or neurobiological findings. It was concluded that IA and ALB are similar conditions, and autism has a wide continuum of clinical expressions.

7.186. Mohandas, T.K., Park, J.P., Spellman, R.A., Filiano, J.J., Mamourian, A.C., Hawk, A.B., Belloni, D.R., Noll, W.W., Moeschler, J.B. "Paternally derived de novo interstitial duplication of proximal 15q in a patient with developmental delay." *Am J Med Genet* 1999 Feb 12;82(4):294-300.

Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03767, USA.

Interstitial duplications of proximal 15q containing the Prader-Willi syndrome/Angelman syndrome (PWS/AS) region have been found in patients with autism or atypical autism. In these cases with an abnormal phenotype, the duplications were maternally derived. Paternal origin of the duplication has been associated with a normal phenotype. We report on a patient who presented with nonspecific developmental delay and partial agenesis of the rostral corpus callosum. Fluorescence in situ hybridization (FISH) studies using probes specific for the PWS/AS region demonstrated a double signal on one chromosome 15, indicating the presence of an interstitial duplication of proximal 15q involving the PWS/AS region in the patient. Parental chromosomes were normal with FISH studies. Methylation analysis at exon alpha of the SNRPN locus showed a maternal band at 4.2 kb and a paternal band of apparent double intensity at 0.9 kb, suggestive of one copy of the maternal allele and two copies of the paternal allele in the patient. Microsatellite analysis was informative at the GABRB3 locus in the family, which showed the inheritance of two different paternal alleles and a maternal allele in the patient consistent with the origin of this duplication from an unequal crossing over between the two chromosome 15 homologs in the father. This is the first report of an abnormal phenotype associated with a paternally derived duplication of proximal 15q shown to contain the PWS/AS region by molecular techniques.

7.187. Stadtler, A.C., Burke, P. "A group treatment approach to failure to toilet train: the case of Max." *Clin Excell Nurse Pract* 1998 Mar;2(2):83-7.

Children's Hospital, Medical Diagnostic Clinics, Boston, MA 02115, USA.

Toilet training is a major developmental milestone for children and parents. Accurate statistics on the prevalence of toilet-

training failure do not exist; however, it is estimated that approximately 4% of 4-year-olds are not bowel trained. A number of biopsychosocial and developmental factors can interfere with toilet training. Frequently, a cycle of withholding and constipation with painful bowel movements and/or overflow incontinence ensues. A case study of a 4-year-old boy with encopresis and pervasive developmental disorder will highlight an interdisciplinary team's approach to helping children (4-6 years old) toilet train. Along with individual patient care management, parents and children attended (separately) a six-session medical and psychoeducational group called "Toilet School." This group model employs the principles of behavior modification, the concepts of children's preoperational thinking, and a philosophy of care that values collaborative relationships between caregivers and families.

7.188. Howe, M.J., Davidson, J.W., Sloboda, J.A. "Innate talents: reality or myth?" *Behav Brain Sci* 1998 Jun;21(3):399-407; discussion 407-42. Publication Types: Review, Review, Tutorial.

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Talents that selectively facilitate the acquisition of high levels of skill are said to be present in some children but not others. The evidence for this includes biological correlates of specific abilities, certain rare abilities in autistic savants, and the seemingly spontaneous emergence of exceptional abilities in young children, but there is also contrary evidence indicating an absence of early precursors of high skill levels. An analysis of positive and negative evidence and arguments suggests that differences in early experiences, preferences, opportunities, habits, training, and practice are the real determinants of excellence.

7.189. Turk, J., Cornish, K. "Face recognition and emotion perception in boys with fragile-X syndrome." *J Intellect Disabil Res* 1998 Dec;42 (Pt 6):490-9.

Department of Psychiatry, St George's Hospital Medical School, London, UK.

Two independent and complementary studies were conducted to assess the ability of boys with fragile-X syndrome to recognize facial and emotional expressions. Both studies failed to find any specific deficits associated with fragile-X syndrome. The performance of the test group was comparable to the level of subjects with intellectual disability and subjects of average cognitive development matched for intellectual ability. This suggests that chronological age and intellectual level are unlikely to explain the findings. The results are discussed in the context of the controversy surrounding the relationship between autism and fragile-X syndrome. The findings are consistent with fragile-X individuals having a profile of social, communicatory and ritualistic disturbances, which in some ways may differ from those found in individuals who have more typical autistic spectrum disorders.

7.190. Gombosi, P.G. "Parents of autistic children. Some thoughts about trauma, dislocation, and tragedy." *Psychoanal Study Child* 1998;53:254-75.

Department of Psychiatry, Harvard Medical School, USA.

People who suffer unexpected trauma often go through periods of intense dislocation, which resolve into a new sense of self-organization, marked by a distinct sense of tragedy. Parents of autistic children are given as an example of this phenomenon. Dislocation is described as not just part of the mourning process but as the result of the disturbance of both the internal and external components that maintain ego autonomy. Some suggestions are given for working with traumatized parents to help them reorient themselves within this dislocation and to foster and preserve their sense of being "good enough" parents.

7.191. Collacott, R.A., Cooper, S.A., Branford, D., McGrother, C. "Epidemiology of self-injurious behaviour in adults with learning disabilities." *Br J Psychiatry* 1998 Nov;173:428-32.

Rockingham Forest NHS Trust, Kettering.

BACKGROUND: There have been few epidemiological studies of the disabling and poorly understood disorder self-injurious behaviour among adults with learning disabilities. **METHOD:** Interviews were undertaken with the carers of adults known to the Leicestershire Learning Disabilities Register (n = 2277). The Disability Assessment Schedule was used and information was also collected on demographic characteristics, developmental and physical status. **RESULTS:** Self-injurious behaviour was present in 17.4% of the population. In 1.7% self-injurious behaviour occurred frequently and was severe. There was no gender difference between those with and without self-injurious behaviour. Both the chronological age and developmental quotient of individuals with self-injurious behaviour were lower than those of individuals without self-injurious behaviour. Autistic symptoms were more common among those with self-injurious behaviour. The association of self-injurious behaviour with a wide range of other maladaptive behaviours was highly significant. Logistic regression analysis retained age, developmental quotient, hearing status, immobility and number of autistic symptoms as explanatory variables for self-injurious behaviour. **CONCLUSIONS:** Self-injurious behaviour is a prevalent and disabling disorder among adults with learning disabilities.

7.192. Kobayashi, R. "Perception metamorphosis phenomenon in autism." *Psychiatry Clin Neurosci* 1998 Dec;52(6):611-20.

Tokai University School of Health Sciences, Isehara, Kanagawa, Japan.

It is well known that various perceptual abnormalities exist in autism. However, because perceptual phenomena are intersubjective, a phenomenological approach is required for getting hold of the reality of the modes of perception involved in autism. From this standpoint, the author has proposed the concept of 'perception metamorphosis phenomenon' (PMP)

as the mode of perception peculiar to autistics. This mode of perception is notable to some degree in infancy and adolescence, and points to the appearance of behavior that is indicative of the environmental world being perceived in a manner different from before by the autistic child. The phenomenon has been classified into three basic categories according to the aspect of perception: (i) visual PMP; (ii) auditory PMP; and (iii) situational PMP. The proposal of this concept was made with the objective of capturing the onset of autism or the mechanism of appearance of the various symptoms from a more phenomenological viewpoint, to serve as a possible starting point for understanding the inner world of autistics. The proposal was made emphasizing the validity of this approach in mapping out new therapeutic approaches and for re-investigating the relationship between autism and schizophrenia.

7.193. Kemner, C., Verbaten, M.N., Koelega, H.S., Camfferman, G., van Engeland, H. "Are abnormal event-related potentials specific to children with ADHD? A comparison with two clinical groups." *Percept Mot Skills* 1998 Dec;87(3 Pt 1):1083-90.

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Children with attention deficit disorder and hyperactivity (ADHD) were compared with two other clinical groups, namely, children with autism and children with dyslexia, with respect to several peaks of the ERP. By using these other clinical groups, it was studied whether amplitude differences between children and ADHD and normal control children, which were found in an earlier study, were specific to children with ADHD. ERPs were measured in response to stimuli in an auditory and a visual oddball task. Only with respect to the P3 and Pz, measured in response to deviant auditory stimuli, did the children with ADHD show smaller amplitudes than both autistic children and those with dyslexia. It was concluded that a smaller amplitude of this peak is specific to children with ADHD.

7.194. Akefeldt, A., Ekman, R., Gillberg, C., Mansson, J.E. "Cerebrospinal fluid monoamines in Prader-Willi syndrome." *Biol Psychiatry* 1998 Dec 15;44(12):1321-8.

Department of Child and Adolescent Psychiatry, University of Goteborg, Molndal.

BACKGROUND: The behavioral phenotype of Prader-Willi syndrome (PWS) suggests hypothalamic dysfunction and altered neurotransmitter regulation. The purpose of this study was to examine whether there was any difference in the concentrations of monoamine metabolites in the cerebrospinal fluid (CSF) in PWS and non-PWS comparison cases. **METHODS:** The concentration of monoamine metabolites in CSF was determined in 13 children and adolescents with PWS diagnosed on clinical and genetic criteria. The concentrations were compared with those from 56 comparison cases in healthy and other contrast groups. **RESULTS:** The concentrations of dopamine and particularly serotonin

metabolites were increased in the PWS group. The differences were most prominent for 5-hydroxyindoleacetic acid. The increased concentrations were found in all PWS cases independently of age, body mass index, and level of mental retardation. CONCLUSIONS: The findings implicate dysfunction of the serotonergic system and possibly also of the dopamine system in PWS individuals, and might help inform future psychopharmacologic studies.

7.195. Bondy, A.S., Frost, L.A. "The picture exchange communication system." *Semin Speech Lang* 1998;19(4):373-88; quiz 389, 424. Publication Types: Review, Review, Tutorial.

Pyramid Educational Consultants, Inc., Cherry Hill, NJ 08003, USA.

The Picture Exchange Communication System (PECS) was developed as a means to teach children with autism and related developmental disabilities a rapidly acquired, self-initiating, functional communication system. Its theoretical roots combine principles from applied behavior analysis and guidelines established within the field of alternative and augmentative communication. This approach has several potential advantages relative to imitation-based strategies (both vocal and gestural) and symbol selection strategies. The system begins with the exchange of simple icons but rapidly builds "sentence" structure. The system also emphasizes developing the request function prior to developing responding to simple questions and commenting. The development of requesting with a sentence structure also permits the rapid development of attributes more traditionally taught within a receptive mode. The relationship between the introduction of PECS and various other behavioral issues (i.e., social approach and behavior management) as well as its relationship to the codevelopment of speech are reviewed.

7.196. Yirmiya, N., Erel, O., Shaked, M., Solomonica-Levi, D. "Meta-analyses comparing theory of mind abilities of individuals with autism, individuals with mental retardation, and normally developing individuals." *Psychol Bull* 1998 Nov;124(3):283-307. Publication Types: Meta-Analysis.

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A deficit in theory of mind (ToM) abilities has been described as the core deficit in autism. The authors performed 3 meta-analyses, comparing ToM abilities of individuals with autism, individuals with mental retardation (MR), and normally developing individuals. Results indicated that individuals with autism and MR have impaired ToM abilities. The etiology associated with MR (i.e., Down syndrome, undifferentiated etiology) was found to be an important moderator variable. Chronological age (CA) and verbal mental age (VMA) of the normally developing children and CA, VMA, and performance mental age of individuals with MR, and type of matching between the groups were also found to be moderator variables. Discussion focuses on the implication of the findings and emphasizes the need to consider the specific etiology of comparison groups when studying abilities and impairments of individuals with autism and MR.

7.197. Rapin, I. "Understanding childhood language disorders." *Curr Opin Pediatr* 1998 Dec;10(6):561-6.

Rose F. Kennedy Center for Research in Mental Retardation and Human Development, Albert Einstein College of Medicine, Bronx, NY 10461, USA.

Developmental language disorders exist in 5% to 10% of preschoolers and have strong genetic implications. There are several variants of dysphasia: mixed receptive/expressive, expressive, or higher order language processing. Preschool children with pervasive developmental disorders are dysphasic as well as autistic. Some undergo a language and behavioral regression, most often as toddlers. The role of subclinical epilepsy in this regression is unknown because it is often ignored. Most dysphasic children speak by schoolage but are at substantial risk for reading/academic difficulty. Powerful new techniques to image the brain during language have no place in the routine workshop of children with dysphasia with or without autism.

7.198. Lee, A., Hobson, R.P. "On developing self-concepts: a controlled study of children and adolescents with autism." *J Child Psychol Psychiatry* 1998 Nov;39(8):1131-44. Publication Types: Clinical Trial, Controlled Clinical Trial.

Developmental Psychopathology Research Unit, Tavistock Clinic, and University College London Medical School, UK.

This study employed the self-understanding interview of Damon and Hart (1988) to assess the self-concepts of two groups of children and adolescents: a group of individuals with autism and a group of nonautistic mentally retarded individuals who were matched for age and for verbal ability. On the basis of an hypothesis concerning the interpersonal origins of social and psychological self-concepts (Hobson, 1990; Neisser, 1988), it was predicted that the participants with autism would show a relative dearth of such concepts in their talk about themselves. In accordance with our predictions, there was a significant group difference in the number and quality of statements that fell into the social category of self-concept; contrary to our predictions, however, there was no group difference in the number of statements that fell into the psychological category. In addition, although there were not significant group differences in the overall production of verbally expressed concepts concerning self-attributes of a physical, active, or psychological kind, even within these categories individuals with autism made fewer references to social interactions or qualities. These results are discussed with regard to theories of self-concept development in typically developing as well as autistic and mentally retarded individuals, and with reference to the limitations of interpersonal understanding ("theory of mind") in people with autism.

7.199. Hollander, E. "Treatment of obsessive-compulsive spectrum disorders with SSRIs." *Br J Psychiatry Suppl* 1998;(35):7-12. Publication Types: Review, Review, Tutorial.

Mount Sinai School of Medicine, New York, NY 10029, USA.

BACKGROUND: Obsessive-compulsive spectrum disorders

(OCSDs) are now recognised as distinct diagnostic entities related to obsessive-compulsive disorder (OCD). The features of OCSDs and OCD overlap in many respects including demographics, repetitive intrusive thoughts or behaviours, comorbidity, aetiology and preferential response to anti-obsessional drugs such as the selective serotonin reuptake inhibitors (SSRIs). **METHOD:** Literature was reviewed and preliminary data from various studies were re-examined to assess the relationship between compulsivity and impulsivity, and between OCD and OCSDs. **RESULTS:** OCSDs include both compulsive and impulsive disorders and these can be viewed as lying at opposite ends of the dimension of risk avoidance. Compulsiveness is associated with increased frontal lobe activity and increased serotonergic activity, while impulsiveness is associated with reduced activity of these variables. Neural circuits affected by serotonergic pathways have been identified and pharmacological challenge of OCSD patients with serotonin receptor agonists have supported the involvement of serotonergic processes. **CONCLUSIONS:** SSRIs such as fluvoxamine have established efficacy in OCD and preliminary studies indicate that they are also effective in OCSDs. The features of three specimen OCSDs—body dysmorphic disorder, pathological gambling and autism—and their treatment with SSRIs are reviewed.

7.200. Lowe, K., Felce, D., Perry, J., Baxter, H., Jones, E. "The characteristics and residential situations of people with severe intellectual disability and the most severe challenging behaviour in Wales." *J Intellect Disabil Res* 1998 Oct;42 (Pt 5):375-89.

Welsh Centre for Learning Disabilities Applied Research Unit, University of Wales College of Medicine, Cardiff, UK.

A total population study of people in Wales with severe intellectual disability and the most severe challenging behaviour was undertaken to identify their characteristics, and the nature of their residential arrangements and service support. Forty-one participants were identified: five living in family homes, 17 in community housing, 17 in hospitals and two in hostels. The family home group had slightly higher adaptive behaviour scores than residents in community housing. Both groups had significantly higher scores than the hospital and hostel residents combined. Assessments of challenging behaviour showed the groups to be similar and to have a considerable range and extent of severely problematic behaviour. Co-occurrence of several forms of frequent severe problem behaviour was the norm and there was a marked association with social impairment. The five people living in their family homes had nominated service keyworkers, but reported professional input was low. The residential situations comprised two main service types: (1) traditional services, which were characterized by large living unit and facility size, atypical architectural design, relative isolation from the community, a greater level of buildings adaptations, low staff:resident ratios, a relatively high percentage of qualified staff, and a relative absence of systematic approaches to goal planning and structured activity; and (2) new community houses, which were characterized by small size, domestic design, location within

the community, a lower level of buildings adaptations, much higher staff:resident ratios, and less emphasis on qualified staff but a greater emphasis on systematic working methods. Community settings were similar in having 'specialist' resident groupings based on challenging behaviour or conditions like autism in which challenging behaviours are common. A policy to provide for people with these characteristics being resettled from traditional settings in this way seems to have been established.

7.201. Barnes, J., Kroll, L., Lee, J., Jones, A., Stein, A. "Communication about parental illness with children who have learning disabilities and behavioural problems: three case studies." *Child Care Health Dev* 1998 Nov;24(6):441-56.

Leopold Muller Department of Child and Family Mental Health, Royal Free and University College Medical School of University College London, UK.

Parental illness can have a profound impact on family relationships and children's behaviour. The amount and nature of communication between parents and children about the illness can play an important role, both positively and negatively, in mediating the outcomes. When children have a disability, families can be reluctant to communicate with them about family difficulties. They are often concerned about the impact that parental unavailability may have on their child's life. This paper reports on three families in which the mother was diagnosed with breast cancer and one child in the family had a disability. The extent and specific characteristics of their communication about the maternal illness with their children, behavioural changes in the children, explanations of communication strategies and attributions of behavioural changes are described. Family coping strategies are examined with reference to Lazarus's process model of stress and coping and the use of either problem-focused or emotion-focused strategies. Implications for possible clinical interventions are proposed. In particular it is suggested that families be offered consultation about: what children might understand; ways in which to communicate effectively; and strategies for coping with the long-term implications of serious parental illness.

7.202. Klein, U., Nowak, A.J. "Autistic disorder: a review for the pediatric dentist." *Pediatr Dent* 1998 Sep-Oct;20(5):312-7. Publication Types: Review, Review, Tutorial.

Dental publications on autism have been sparse since the first comprehensive article geared for the dental profession. New findings on the etiology of autistic disorder (AD) have been discovered, suggesting that it is an organic disorder characterized by abnormalities in the brain, especially the cerebellum and limbic system. This article summarizes the latest medical findings on the etiology, diagnosis, and treatment approaches of AD, and reviews the dental literature since 1969. The main dental topics reviewed are: oral health status and dental needs of patients with AD, characteristics of patients with AD, and self-injurious behavior (SIB) in the context of AD. Clinical behavior-management issues such as pharmacological and communicative techniques and physical restraint and desensitization are described. The affect of the

dental office's environment and appointment structure on a patient with AD are presented.

7.203. Stone, V.E., Baron-Cohen, S., Knight, R.T. "Frontal lobe contributions to theory of mind." *J Cogn Neurosci* 1998 Sep;10(5):640-56.

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"Theory of mind," the ability to make inferences about others' mental states, seems to be a modular cognitive capacity that underlies humans' ability to engage in complex social interaction. It develops in several distinct stages, which can be measured with social reasoning tests of increasing difficulty. Individuals with Asperger's syndrome, a mild form of autism, perform well on simpler theory of mind tests but show deficits on more developmentally advanced theory of mind tests. We tested patients with bilateral damage to orbito-frontal cortex (n = 5) and unilateral damage in left dorsolateral prefrontal cortex (n = 5) on a series of theory of mind tasks varying in difficulty. Bilateral orbito-frontal lesion patients performed similarly to individuals with Asperger's syndrome, performing well on simpler tests and showing deficits on tasks requiring more subtle social reasoning, such as the ability to recognize a faux pas. In contrast, no specific theory of mind deficits were evident in the unilateral dorsolateral frontal lesion patients. The dorsolateral lesion patients had difficulty only on versions of the tasks that placed demands on working memory.

7.204. Tallal, P., Merzenich, M., Miller, S., Jenkins, W. "Language learning impairment: integrating research and remediation." *Scand J Psychol* 1998 Sep;39(3):197-9.

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Timing cues present in the acoustic waveform of speech provide critical information for the recognition and segmentation of the ongoing speech signal. Research has

demonstrated that deficient temporal perception rates, that have been shown to specifically disrupt acoustic processing of speech, are related to specific language-based learning impairments (LLI). Temporal processing deficits correlate highly with the phonological discrimination and processing deficits of these children. Electrophysiological single cell mapping studies of sensory cortex in brains of primates have shown that neural circuitry can be remapped after specific, temporally cohesive training regimens, demonstrating the dynamic plasticity of the brain. Recently, we combined these two lines of research in a series of studies that addressed whether the temporal processing deficits seen in LLIs can be significantly modified through adaptive training aimed at reducing temporal integration thresholds. Simultaneously, we developed a computer algorithm that expanded and enhanced the brief, rapidly changing acoustic segments within ongoing speech and used this to provide intensive speech and language training exercises to these children. Results to date from two independent laboratory experiments, as well as a large national clinical efficacy trial, demonstrate that dramatic improvements in temporal integration thresholds, together with speech and language comprehension abilities of LLI children, results from training with these new computer-based training procedures.

7.205. Frith, U. "Cognitive deficits in developmental disorders." *Scand J Psychol* 1998 Sep;39(3):191-5. Publication Types: Review, Review, Tutorial.

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The existence of specific developmental disorders such as dyslexia and autism raises interesting issues about the structure of the normally developing mind. In these disorders distinct cognitive deficits can explain a range of behavioural impairments and have the potential to be linked to specific brain abnormalities. One possibility is that there are specific mechanisms dedicated to particular types of information processing. These mechanisms may function independently of more general information processing systems and may have a distinct anatomical basis in the brain.