

ADI/ADI-R Bibliography with Abstracts
1989-Current

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I. Major Articles Describing the ADI-R / ADI

Le Couteur, A., M. Rutter, et al. (1989). "Autism Diagnostic Interview: A standardized investigator-based instrument." *Journal of Autism & Developmental Disorders*, 19(3): 363-387.

Describes (1) the development of a new standardized investigator-based interview for use in the differential diagnosis of pervasive developmental disorders and (2) a diagnostic algorithm (using International Classification of Diseases--10th Edition [ICD-10] criteria) based on its use. Good interrater reliability for algorithm items was shown between 4 raters, 2 in Canada and 2 in the UK, who rated 32 videotaped interviews. The items also significantly discriminated between 16 autistic (mean age 13.26 yrs; IQ 30-93) and 16 nonautistic (mean age 12.28 yrs; IQ 43-71) mentally handicapped Ss. The algorithm based on ICD-10 identified all 16 autistic Ss and none of the 16 nonautistic Ss. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Lord, C., M. Rutter, et al. (1994). Autism Diagnostic Interview-Revised - a Revised Version of a Diagnostic Interview for Caregivers of Individuals with Possible Pervasive Developmental Disorders. *Journal of Autism and Developmental Disorders*, 24(5): 659-685.

Describes the Autism Diagnostic Interview-Revised (ADI-R), a revision of the Autism Diagnostic Interview, a semistructured, investigator-based interview for caregivers of children and adults for whom autism or pervasive developmental disorders is a possible diagnosis. The revised interview has been reorganized, shortened, modified to be appropriate for children with mental ages from about 18 months into adulthood and linked to ICD-10 and DSM-IV criteria. Psychometric data are presented for a sample of preschool children.

Lord, C. (1991). "Methods and measures of behavior in the diagnosis of autism and related disorders." *Psychiatric Clinics of North America*, 14(1): 69-80.

In the past 5 years, diagnostic schemes for autism and related psychiatric disorders have become increasingly sophisticated. However, within these diagnostic frameworks, no specific assessment procedures have been prescribed. On the other hand, work has continued in the development of empirically rooted instruments for the diagnosis and screening of autism and related disorders. The need for diagnostic methods and instruments that incorporate current diagnostic criteria, that use methods specifically aimed at gleaning information about the communicative and social deficits associated with autism, and that differentiate autism from related disorders is discussed. Two new instruments that attempt to fill this need, the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule, are briefly described. [References: 48]

Articles Presenting Research on the ADI-R Published 2005

Bolte, S., & Poustka, F. (2005). Psychodiagnostic instruments for the assessment of autism spectrum disorders. *Zeitschrift Fur Kinder-Und Jugendpsychiatrie Und Psychotherapie*, 33(1), 5-14.

Objectives: Established scales for the early detection and general diagnostics of autism will be reviewed with a focus on the instruments available in German. Methods: All questionnaires, observation scales and interviews for the assessment of autism and associated conditions found in a search of Medline, PsychInfo, Psyn dex and Google up to May 2004 are quoted. Instruments adapted and developed for the German-speaking countries are presented in more depth. Results: An increasing number of reliable national and international scales for the assessment of disorders of the autism spectrum are available. Currently a combination of the Social Communication Questionnaire (SCQ), the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) is regarded as the standard for a psychometrically based diagnosis of autism. Conclusions: For certain diagnostic groups and issues there continues to be a need for German-language instruments. Particularly scales for the assessment of the broader phenotype of autism, as well as instruments that are more sensitive to change would be desirable for Outcome measurement and intervention evaluation.

Ozonoff, S., B. L. Goodlin-Jones, et al. (2005). "Evidence-based assessment of autism spectrum disorders in children and adolescents." Journal of Clinical Child and Adolescent Psychology 34(3): 523-540.

This article reviews evidence-based criteria that can guide practitioners in the selection, use, and interpretation of assessment tools for autism spectrum disorders (ASD). As Mash and Hunsley (2005) discuss in this special section, evidence-based assessment tools not only demonstrate adequate psychometric qualities, but also have relevance to the delivery of services to individuals with the disorder (see also Hayes, Nelson, & Jarrett, 1987). Thus, we use what is known about the symptoms, etiologies, developmental course, and outcome of ASD to evaluate the utility of particular assessment strategies and instruments for diagnosis, treatment planning and monitoring, and evaluation of outcome. The article begins with a review of relevant research on ASD. Next we provide an overview of the assessment process and some important issues that must be considered. We then describe the components of a core (minimum) assessment battery, followed by additional domains that might be considered in a more comprehensive assessment. Domains covered include core autism symptomatology, intelligence, language, adaptive behavior neuropsychological functions, comorbid psychiatric illnesses, and contextual factors (e.g., parent well-being, family functioning, quality of life). We end with a discussion of how well the extant literature meets criteria for evidence-based assessments.

Published 2004

Bolte, S. and F. Poustka (2004). "The German form of the Autism Diagnostic Observation Schedule (ADOS): first results on reliability and validity." *Zeitschrift Fur Kinder-Und Jugendpsychiatrie Und Psychotherapie*, 32(1), 45-50.

Objective: To examine the psychometric properties of the German version of the Autism Diagnostic Observation Schedule (ADOS). Methods: Interrater and retest reliability, internal consistency, convergent and diagnostic validity were determined in a total sample of 137 subjects with autism, 23 with atypical autism or pervasive developmental disorder not otherwise specified, 16 with Asperger-syndrome and 13 with other psychiatric disorders. Results: Interrater and retest reliability on the level of diagnosis ($\kappa(w) = 1.00$ and $.62$ and raw-scores ($r(u) = .84$ and $.79$) were good. Likewise, the internal consistency of the algorithm scale communication and social interaction of modules 1 to 4 was fair ($r(u) = .78$ to $.89$). The categorical convergence for autism between the ADOS and the Autism Diagnostic Interview-Revised (ADI-R) reached 79% ($\kappa = .23$), with their corresponding subscales correlating moderately ($r(tc) = .31$ to $.45$). The concordance of the ADOS judgment and the clinical consensus diagnosis was 77% ($\kappa(w) = .37$), with a sensitivity of the ADOS of 90.4% and a specificity of 48.1% regarding the discrimination of autism and other autistic disorders. Conclusions: The ADOS is a reliable and sufficiently sensitive diagnostic tool in the assessment of autistic disorders. For ICD-10/DSM-IV classification and to ensure a high specificity of diagnosis additional information concerning repetitive, stereotyped behavior and early development (e.g. taken from the ADI-R) has to be collected.

Constantino, J.N., Gruber, C.P., Davis, S., Hayes, S., Passanante, N., & Przybeck, T. (2004). The factor structure of autistic traits. *Journal of Child Psychology and Psychiatry*, 45(4), 719-726.

Background: Although DSM-IV requires symptoms in three criterion domains for a diagnosis of autistic disorder, the extent to which those domains are phenotypically independent is an unanswered and important question. The identification of endophenotypes_ of the autistic syndrome may be very useful for genetic and neurobiologic studies of autism, but only if they represent truly independent sub domains of the disorder. Methods: In this study we examined the factor structure of autistic traits using data from 226 child psychiatric patients with and without pervasive developmental disorders, employing cluster analysis of data from the Autism Diagnostic Interview-Revised (ADI-r) and principal components factor analysis of data from the Social Responsiveness Scale (SRS, a quantitative genetic measure of autistic traits formerly known as the Social Reciprocity Scale). Results: The results were consistent with the existence of a singular, continuously distributed underlying factor, resulting in disparate phenotypic manifestations across the three criterion domains for autistic disorder (social deficits, language deficits, and repetitive/stereotypic behaviors). Conclusion: The analyses generally failed to support the existence of independent sub domains of dysfunction in autism spectrum conditions. Future studies of the association between genetic/neurobiologic markers and autistic symptomatology may be enhanced by approaches which consider autistic symptoms as quantitative traits, and which are

informed by ongoing research on the development and phenomenology of core deficiencies in reciprocal social behavior.

de Bildt, A., S. Sytema, et al. (2004). "Interrelationship between autism diagnostic observation schedule-generic (ADOS-G), autism diagnostic interview-revised (ADI-R), and the diagnostic and statistical manual of mental disorders (DSM-IV-TR) classification in children and adolescents with mental retardation." *Journal of Autism and Developmental Disorders*, 34(2): 129-137.

The interrelationship between the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule-Generic (ADOS-G) and clinical classification was studied in 184 children and adolescents with Mental Retardation (MR). The agreement between the ADI-R and ADOS-G was fair, with a substantial difference between younger and older children (5-8 vs. 8+ years). Compared with the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) classification of Autistic Disorder (AD) and Pervasive Developmental Disorder (PDD), both instruments measure AD or PDD validly and reliably. Even in low-functioning children the interrelationship between the instruments and the clinical classification was satisfactory. The combination of ADI-R and ADOS-G identifies AD or PDD, as described in the DSM-IV-TR, most appropriately. Both instruments seem to be of great value in the diagnostic process of PDD in children and adolescents with MR.

Published 2003

de Bildt, A., S. Sytema, et al. (2003). "Measuring pervasive developmental disorders in children and adolescents with mental retardation: A comparison of two screening instruments used in a study of the total mentally retarded population from a designated area." *Journal of Autism and Developmental Disorders*, 33(6): 595-605.

The performance of two screening instruments for Pervasive Developmental Disorders was studied in the total population of participants with mental retardation between 4 and 18 years ($n = 1059$) in Friesland, a northern province of the Netherlands. Parents completed the Autism Behavior Checklist (ABC), staff completed the Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS). The screening instruments were related to the Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule - Generic for 184 participants. The agreement between ABC and PDD-MRS was fair ($\kappa = .24$). The ABC had a better criterion-related validity compared with the Autism Diagnostic Interview - Revised, and the PDD-MRS compared to the Autism Diagnostic Observation Schedule - Generic. However, related to the clinical classification, both instruments performed equally well. Concluding, the ABC and PDD-MRS partially identify the same cases related to external criteria. In addition, each instrument has its own contribution. Both instruments are valuable in detecting children who are at high risk for PDD.

Cuccaro, M. L., Y. J. Shao, et al. (2003). "Factor analysis of restricted and repetitive behaviors in autism using the Autism Diagnostic Interview-R." *Child Psychiatry & Human Development*, 34(1): 3-17.

The current study examined the factor structure of restricted and repetitive behaviors (RRB) in children with autism. Factor extraction procedures of 12 items from the Autism Diagnostic Interview-Revised (ADI-R) were applied in N = 207 individuals with autism. Two interpretable factors were identified: Factor 1-repetitive sensory motor actions and Factor 2-resistance to change. There was a significant negative correlation between an index of level of adaptive functioning and Factor 1. Intraclass correlations were not significant for either factor in a subset of families with two or more siblings with autism (multiplex). No differences in scores were apparent for either factor when multiplex families and families containing only one affected individual with autism (singleton) were compared. RRB in autism are represented by two distinct factors which may reflect two separate groups within autism. Defining subgroups within autism will allow for reduction of clinical heterogeneity and enhance our ability to dissect the genetic etiology of this complex disorder.

Goldberg, W.A., Osann, K., Filipek, P.A., Laulhere, T., Jarvis, K., Modahl, C., Flodman, P., & Spence, M.A. (2003). Language and other regression: Assessment and timing. *Journal of Autism and Developmental Disorders*, 33(6), 607-616.

Understanding of regression in autism has been hampered by variability in parental and clinical recognition and reporting of lost skills. This study introduced an instrument, the Regression Supplement Form, intended to supplement the Autism Diagnosis Interview-Revised and yield precise information about the types and timing of regression and events concurrent with loss and regain of skills. Data were collected from parents of 44 children (38 male, 6 female; mean age = 6 years) with Autistic Spectrum Disorder (37 Autistic Disorder, 7 Pervasive Developmental Disorder-Not Otherwise Specified). Parental responses on the Autism Diagnosis Interview-Revised indicated loss of skills during early development. The profile of regression that emerged included loss of skills between 18 and 21 months, on average, with language-only regression less common than loss of other, nonlanguage skills only or of full regression (loss of language and other skills). The onset of regression typically was gradual in nonlanguage areas and split between gradual and sudden loss for language skills. Some of the children were developing atypically before they lost other, nonlanguage skills, that is, their age at first words was delayed until age 2 years or older. Parents tended to attribute loss to medical factors such as immunizations. Many of the children regained some of the lost skills when they were 3.5-5 years of age, with therapeutic and instructional interventions given credit for the regain.

Hansen, R. L., B. Goodlin-Jones, et al. (2003). "Discrepancies in the diagnosis of autism by ADOS-G and ADI-R criteria in fragile 3L." *Journal of Investigative Medicine*, 51: S113-S113.

Saemundsen, E., P. Magnusson, et al. (2003). "Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale: Convergence and discrepancy in diagnosing autism." *Journal of Autism and Developmental Disorders*, 33(3): 319-328.

The agreement between the Autism Diagnostic Interview - Revised (ADI-R) and the Childhood Autism Rating Scale (CARS) was investigated in the diagnostic

assessment of 54 children aged 22 - 114 months referred for possible autism. The observed agreement between the two systems was 66.7% (Cohen's kappa =.40) when the ADI-R definition for autism was applied (i.e., scores reaching cutoff in three domains on the ADI-R), but increased considerably with less stringent criteria; that is, scores reaching cutoffs in two domains and in one domain on the ADI-R. As predicted, the CARS identified more cases of autism than the ADI-R. Children classified as autistic according to both instruments had significantly lower IQ/DQ and more severe autistic symptomatology than those classified with the CARS only.

Tadevosyan-Leyfer, O., M. Dowd, et al. (2003). "A principal components analysis of the autism diagnostic interview-revised." *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(7): 864-872.

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 VAR-CLUS. 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.

Seltzer, M. M., Krauss, M.W., Shattuck, P.T., Orsmond, G., Swe, A., & Lord, C. (2003). The symptoms of autism spectrum disorders in adolescence and adulthood. *Journal of Autism and Developmental Disorders*, 33(6): 565-581.

This article describes the symptoms of autism spectrum disorders (ASD) manifested by 405 individuals between the ages of 10 and 53 years, all of whom had an ASD diagnosis. Data were collected using the Autism Diagnostic Interview -Revised (ADI-R) to assess the pattern of autism symptoms in adolescence and adulthood. Findings include that although virtually all sample members met the criteria for Autistic Disorder earlier in their childhood, just over half (54.8%) would have met autism criteria if current scores were used to complete the diagnostic algorithm; that adolescents were more likely to improve in the Reciprocal Social Interaction domain than the adults, whereas the adults were more likely to improve in the Restricted, Repetitive Behaviors and Interests domain, and there were no differences in severity of symptoms between cohorts in the Communication domain; and that individual symptoms showed unique trajectories, with greatest symptom abatement between lifetime and current ADI-R ratings for speaking in at least three-word phrases and the least symptom improvement for having friendships. Findings were interpreted in the context of life course development, reformulations of diagnostic criteria, and changing service contexts for individuals with autism spectrum disorders.

Published 2002

Bishop, D. V. M. and C. F. Norbury (2002). "Exploring the borderlands of autistic disorder and specific language impairment: a study using standardised diagnostic instruments." *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 43(7): 917-929.

Background: Two studies were conducted to test claims that pragmatic language impairment (PLI-previously referred to as semantic-pragmatic disorder) is simply another term for autistic disorder or pervasive developmental disorder not otherwise specified (PDDNOS). Method: In Study 1, 21 children aged from 6 to 9 years with language impairments were subdivided on the basis of the Children's Communication Checklist into 13 cases of pragmatic language impairment (PLI) and eight cases of typical specific language impairment (SLI-T). Parents completed the Autism Diagnostic Interview Revised (ADI-R) and the Social Communication Questionnaire (SCQ), and the children were given the Autism Diagnostic Observation Schedule - Generic (ADOS-G). In Study 2, a further 11 children with SLI-T and 18 with PLI were assessed using the SCQ and ADOS-G. In addition, six children diagnosed with high-functioning autism and 18 normally developing children were assessed. Results: There was good agreement between ADI-R and SCQ diagnoses, but poor agreement between diagnoses based on these parental report measures and those based on ADOS-G. In many children, symptom profiles changed with age. Four PLI children from Study I and one from Study 2 met criteria for autistic disorder on both parental report (ADI-R or SCQ) and ADOS-G. Many of the others showed some autistic features, but there was a subset of children with pragmatic difficulties who were not diagnosed as having autism or PDDNOS by either instrument. These children tended to use stereotyped language with abnormal intonation/prosody, but they appeared sociable and communicative, had normal nonverbal communication, and showed few abnormalities outside the language/social communication domains. Conclusions: Presence of pragmatic difficulties in a child with communication problems should prompt the clinician to evaluate autistic symptomatology, but it is dangerous to assume that all children with pragmatic difficulties have autism or PDDNOS.

Noterdaeme, M., K. Mildenberger, et al. (2002). "Parent information and direct observation in the diagnosis of pervasive and specific developmental disorders." *Autism*, 6(2): 159-168.

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.

II. Articles Using ADI-R / ADI

Published 2006

Battaglia, A., & Carey, J. C. (2006). Etiologic yield of autistic spectrum disorders: A prospective study. *American Journal of Medical Genetics Part C-Seminars in Medical Genetics*, 142C(1), 3-7.

Studies addressing etiologic yield in childhood developmental disabilities have mainly looked at individuals with developmental delay/mental retardation. The few studies addressing the question of etiologic yield in patients with pervasive developmental disorders (PDDs) had a major drawback, in that the enrolled subjects were diagnosed as having the autistic spectrum disorders based only on history and clinical examination, and/or on unspecified instruments. In addition, only some of these patients underwent a complete laboratory evaluation. To investigate the etiologic yield of PDDs, we undertook a large prospective study on subjects selected according to very strict criteria and diagnosed as having PDD based on the present "gold standard" (ADI-R and ADOS-G), and a clinical diagnosis made by a child psychiatrist. Eighty-five (85) patients with PDD and their first degree relatives participated in this study. These patients were selected from a sample of 236 subjects who had received a clinical diagnosis of PDD at the Stella Maris Institute between March 2002 and 2005. Selection criteria for entering the study were: (1) a diagnosis of PDD (with exclusion of the Rett syndrome) confirmed after the administration of the ADI-R (autism diagnostic interview-revised) and the ADOS-G (autism diagnostic observation schedule-generic). In addition, a clinical diagnosis was made by the child psychiatrist, on the basis of presence or absence of DSM-IV symptoms of autism, (2) chronological age between 4 and 18 years, (3) IQ>30; (4) availability of both biologic parents. Patients, 65/85 (76.5%), had autism, 18/85 (21.2%) had PDD-NOS, and the remaining 2/85 (2.3%) had Asperger syndrome. Ages varied between 4 years 2 months and 12 years 5 months (mean 7.6 years), and there was a marked male preponderance (68/85). All subjects underwent various laboratory studies and neuroimaging. With respect to possible etiologic determination, a detailed history and physical examination in this group of patients with PDD was informative in 10.5% (9/85). HRB karyotype was diagnostic in one, and molecular fragile X studies in one child. Brain MRI was informative in two children (2.3%) with relative macrocrania but no neurological features and EEG was helpful in one child, identifying a Landau-Kleffner disorder. Audiometry and brainstem auditory evoked potentials (BAEPs) showed a bilateral sensorineural loss in another child. Metabolic evaluation gave normal results in all subjects. The results suggest an evaluation paradigm with reference to etiologic determination for individuals with PDDs that does not presently justify metabolic or neuroimaging on a screening basis. Recurrence risk, treatment implications, and significant and long-lasting emotional relief for the parents suggest that serious consideration be given to clinical genetic examination, genetic testing, EEG study (during wakefulness and sleep), and audiometry, despite a relatively low yield. (C) 2006 Wiley-Liss, Inc.

Behrmann, M., Avidan, G., Leonard, G. L., Kimchi, R., Luna, B., Humphreys, K., et al. (2006). Configural processing in autism and its relationship to face processing. *Neuropsychologia*, 44(1), 110-129.

Studies of the perceptual performance of individuals with autism have focused, to a large extent, on two domains of visual behavior, one associated with face processing and the other associated with global or holistic processing. Whether autistic individuals differ from neurotypical individuals in these domains is debatable and, moreover, the relationship between the behaviors in these two domains remains unclear. We first compared the face processing ability of 14 adult individuals with autism with that of neurotypical controls and showed that the autistic individuals were slowed in their speed of face discrimination. We then showed that the two groups differed in their ability to derive the global whole in two different tasks, one using hierarchical compound letters and the other using a microgenetic primed matching task with geometric shapes, with the autistic group showing a bias in favor of local information. A significant correlation was also observed between performance on the face task and the configural tasks. We then confirmed the prediction that the ability to derive the global whole is not only critical for faces but also for other objects as well, as the autistic individuals performed more slowly than the control group in discriminating between objects. Taken together, the results suggest that the bias for local processing seen in autistic individuals might have an adverse impact on their ability to process faces and objects. (c) 2005 Elsevier Ltd. All rights reserved.

Chen, G. K., Kono, N., Geschwind, D. H., & Cantor, R. M. (2006). Quantitative trait locus analysis of nonverbal communication in autism spectrum disorder. *Molecular Psychiatry*, 11(2), 214-220.

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome marked by impairments in social interactive functioning and communication skills, and the presence of repetitive and restrictive behaviors. Twin and linkage studies provide evidence that ASD is heritable and genetically complex. Genetic analyses of familial quantitative traits in those with ASD may help to reveal underlying risk genes. We report a quantitative trait locus (QTL) analysis of nonverbal communication (NVC) in 228 families from the autism genetics resource exchange (AGRE) ascertained for at least two siblings with ASD. QTL at 1p13-q12, 4q21-25, 7q35, 8q23-24, and 16p12-13 indicate that genes at these loci may contribute to the variation in NVC among those with ASD. Using the criteria of Lander and Kruglyak, the QTL at 1p13-q12 is 'suggestive', while the other four are 'possible'. To assess whether these QTL are likely to harbor genes contributing specifically to the deficits in NVC, linkage analysis of ASD sibships with the most severe NVC scores was conducted. The sibships were identified by ordered-subset analyses (OSA), and families with the most severe NVC scores displayed lod scores of 3.4 at 8q23-24 and 3.8 at 16p12-13, indicating that these two regions are likely to harbor gene(s) contributing to ASD by predisposing to deficits in NVC.

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., et al. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, 9(1), 28-30.

To examine mirror neuron abnormalities in autism, high-functioning children with autism and matched controls underwent fMRI while imitating and observing emotional expressions. Although both groups performed the tasks equally well, children with autism showed no mirror neuron activity in the inferior frontal gyrus (pars opercularis). Notably, activity in this area was inversely related to symptom severity in the social domain, suggesting that a dysfunctional 'mirror neuron system' may underlie the social deficits observed in autism.

Gomot, M., Bernard, F. A., Davis, M. H., Belmonte, M. K., Ashwin, C., Bullmore, E. T., et al. (2006). Change detection in children with autism: An auditory event-related fMRI study. *Neuroimage*, 29(2), 475-484.

Autism involves impairments in communication and social interaction, as well as high levels of repetitive, stereotypic, and ritualistic behaviours, and extreme resistance to change. This latter dimension, whilst required for a diagnosis, has received less research attention. We hypothesise that this extreme resistance to change in autism is rooted in atypical processing of unexpected stimuli. We tested this using auditory event-related fMRI to determine regional brain activity associated with passive detection of infrequently occurring frequency-deviant and complex novel sounds in a no-task condition. Participants were twelve 10- to 15-year-old children with autism and a group of 12 age- and sex-matched healthy controls. During deviance detection, significant activation common to both groups was located in the superior temporal and inferior frontal gyri. During 'novelty detection', both groups showed activity in the superior temporal gyrus, the temporo-parietal junction, the superior and inferior frontal gyri, and the cingulate gyrus. Children with autism showed reduced activation of the left anterior cingulate cortex during both deviance and novelty detection. During novelty detection, children with autism also showed reduced activation in the bilateral temporo-parietal region and in the right inferior and middle frontal areas. This study confirms previous evidence from ERP studies of atypical brain function related to automatic change detection in autism. Abnormalities involved a cortical network known to have a role in attention switching and attentional resource distribution. These results throw light on the neurophysiological processes underlying autistic 'resistance to change'. (c) 2005 Elsevier Inc. All rights reserved.

Lahaie, A., Mottron, L., Arguin, A., Berthiaume, C., Jemel, B., & Saumier, D. (2006). Face perception in high-functioning autistic adults: Evidence for superior processing of face parts, not for a configural face-processing deficit. *Neuropsychology*, 20(1), 30-41.

Configural processing in autism was studied in Experiment 1 by using the face inversion effect. A normal inversion effect was observed in the participants with autism, suggesting intact configural face processing. A priming paradigm using partial or complete faces served in Experiment 2 to assess both local and configural face processing. Overall, normal priming effects were found in participants with autism, irrespective of whether the partial face primes were intuitive face parts (i.e., eyes, nose, etc.) or arbitrary segments. An exception, however, was that participants with autism showed magnified priming with single face parts relative to typically developing control participants. The present findings argue for intact configural processing in autism along with an enhanced processing for individual face parts. The face-processing peculiarities

known to characterize autism are discussed on the basis of these results and past congruent results with nonsocial stimuli.

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. M. (2006). Neural correlates of executive function in autistic spectrum disorders. *Biological Psychiatry*, 59(1), 7-16.

Background: Some clinical characteristics of high-functioning individuals with autistic spectrum disorder (ASD) such as repetitive stereotyped behaviors, perseveration, and obsessiveness have been related to executive function (EF) deficits, more specifically; to deficits in inhibitory control and set shifting and mediating frontostriatal neural pathways. However, to date, no functional imaging study on ASD has investigated inhibition and cognitive flexibility and no one has related EF brain activation to brain structure. Methods: We compared brain activation (using functional magnetic resonance imaging) in 10 normal intelligence adults with ASD and 12 healthy control subjects during three different EF tasks: 1) motor-inhibition (GO/NO-GO); 2) cognitive interference-inhibition (spatial STROOP); and 3) set shifting (SWITCH). Using voxel-based morphometry, we investigated if cortical areas which were functionally different in people with ASD were also anatomically abnormal. Results: Compared with control subjects, ASD individuals showed significantly increased brain activation in 1) left inferior and orbital frontal gyrus (motor inhibition); 2) left insula (interference-inhibition),- and 3) parietal lobes (set shifting). Moreover, in individuals with ASD, increased frontal gray matter density and increased functional activation shared the same anatomical location. Conclusions: Our findings suggest an association between successful completion EF tasks and increased brain activation in people with ASD. which partially may be explained by differences in brain anatomy.

Seung, H. K., Ashwell, S., Elder, J. H., & Valcante, G. (2006). Verbal communication outcomes in children with autism after in-home father training. *Journal of Intellectual Disability Research*, 50, 139-150.

Background This retrospective study examined the efficacy of in-home father training on the communicative outcomes of children with autism. The in-home training consisted of two components: (1) expectant waiting; and (2) imitation with animation. Methods Efficacy of parent training was examined by measuring the ratio of utterances produced by the parents to the utterances produced by the children and the number of verbal imitations by the parents. Outcomes of the children's verbal production were examined by measuring the number of (1) single word utterances; (2) different words produced; and (3) verbal response to questions. Results Following training there was a decrease in the ratio of parent to child utterances and an increase in (1) the use of imitation by the parents; and (2) the number of single words and different words produced by the children. Discussion Results of this study suggested that the parents had learned to wait for their children to communicate verbally during communicative interactions and to interact more efficiently with their children by using verbal imitation. Overall, the results of this study support the efficacy of parent training that focuses on promotion of social reciprocity, and have important implications for clinicians and future research.

van Lang, N. D. J., Boomsma, A., Sytema, S., de Bildt, A. A., Kraijer, D. W., Ketelaars, C., et al. (2006). Structural equation analysis of a hypothesised symptom model in the autism spectrum. *Journal of Child Psychology and Psychiatry*, 47(1), 37-44.

Background: Several studies showed a different symptom structure underlying the spectrum of autistic-like disorders from the behaviour triad as mentioned in the DSM-IV. In the present study, a hypothesised symptom model for autism was constructed, based on earlier explorative findings, and was put to a confirmatory test. Method: Items from the Autism Diagnostic Interview-Revised (ADI-R) were used to examine the goodness of fit of the DSM-IV model, the hypothesised symptom model, and two additional models for autism. All models were tested in a group of 255 verbal and nonverbal individuals with minor to severe autistic symptomatology. Results: The DSM-IV model encountered estimation problems. Conversely, the hypothesised symptom model had no such problems and proved to have a better fit to the sample data than the two additional models for autism. However, some of the observed variables were weak indicators of the three latent factors in the model. Conclusions: The hypothesised symptom model appeared to be a plausible model in a group of individuals with a broad range of autistic behaviours and levels of functioning. Nevertheless, the stability of the model needs further examination in a larger group of individuals with disorders in the autism spectrum, and with varying degrees of intellectual functioning.

Williams, D. L., Goldstein, G., & Minshew, N. J. (2006). The profile of memory function in children with autism. *Neuropsychology*, 20(1), 21-29.

A clinical memory test was administered to 38 high-functioning children with autism and 38 individually matched normal controls, 8-16 years of age. The resulting profile of memory abilities in the children with autism was characterized by relatively poor memory for complex visual and verbal information and spatial working memory with relatively intact associative learning ability, verbal working memory, and recognition memory. A stepwise discriminant function analysis of the subtests found that the Finger Windows subtest, a measure of spatial working memory, discriminated most accurately between the autism and normal control groups. A principal components analysis indicated that the factor structure of the subtests differed substantially between the children with autism and controls, suggesting differing organizations of memory ability.

Ylisaukko-oja, T., Alarcon, M., Cantor, R. M., Auranen, M., Vanhala, R., Kempas, E., et al. (2006). Search for autism loci by combined analysis of Autism Genetic Resource Exchange and Finnish families. *Annals of Neurology*, 59(1), 145-155.

Objective: Several genome-wide screens have been performed in autism spectrum disorders resulting in the identification of numerous putative susceptibility loci. Analyses of pooled primary data should result in an increased sample size and the different study samples have a potential to strengthen the evidence for some earlier identified loci, reveal novel loci, and even to provide information of the general significance of the locus. The objective of this study was to search for potential susceptibility loci for autism, which are supported by two independent samples. Methods. We performed a combined analysis of the primary genome scan data of the Autism Genetic Resource Exchange (AGRE) and Finnish autism samples to reveal susceptibility loci potentially shared by these study

samples. Results: In the initial combined data analysis, the best loci ($p < 0.05$) were observed at 1p12-q25, 3p24-26, 4q21-31, 5p15-q12, 6q14-21, 7q33-36, 8q22-24, 17p12-q21, and 19p13-q13. The combined analysis of Finnish and AGRE families showed the most promising shared locus on 3p24-26 with nonparametric logarithm of odds (NPL) score of 2.20 ($p = 0.011$). The combined data analysis did not provide increased linkage evidence for the earlier identified loci on 3q25-27 or 17p12-q21. However, the 17p12-q21 locus remained promising also in the combined sample (NPLall = 2.38, $p = 0.0076$). Interpretation: Our study of 314 autism families highlights the importance of further analyses on 3p24-26 locus involving comprehensive molecular genetic analyses of oxytocin receptor gene (OXTR), a positional and functional candidate gene for autism.

Published 2005

Alarcon, M., A. L. Yonan, et al. (2005). "Quantitative genome scan and Ordered-Subsets Analysis of autism endophenotypes support language QTLs." *Molecular Psychiatry* **10**(8): 747-757.

Autism is a neurodevelopmental syndrome with early childhood onset and deficits in three behavioral and cognitive dimensions: language, social skills and repetitive or restrictive behaviors. We hypothesized that using these endophenotypes would provide more power to detect linkage than the diagnosis of autism. Previously, we reported results for a nonparametric quantitative trait locus (QTL) genome scan in 152 families with autism, which revealed a linkage peak related to spoken language on 7q35. Here, we present the results of a nonparametric QTL scan of autism endophenotypes in 291 multiplex families, including the original 152. The strongest evidence for an 'age at first word' QTL was on chromosomes 3q at 147 cM ($Z = 3.10$, $P < 0.001$), and 17q at 93 cM ($Z = 2.84$, $P = 0.002$), both represent novel susceptibility loci for autism endophenotypes. There was also support for a previously identified autism peak on chromosome 17 at 43 cM ($Z = 2.22$, $P = 0.013$) with 'age at first phrase'. The 7q35 language peak was attenuated ($Z = 2.05$, $P = 0.02$) compared with the original finding. To explore the possibility of increased heterogeneity resulting from the addition of 135 families to the sample, we conducted an Ordered-Subsets Analysis on chromosome 7; these results suggest that the 132 autism families with the earliest average age at first word are responsible for the QTL on 7q35. This locus on 7q35 may harbor a gene contributing variability in spoken language that is not uniquely related to language delay in autism.

Baron-Cohen, S., Wheelwright, S., Robinson, J., & Woodbury-Smith, M. (2005). The Adult Asperger Assessment (AAA): A diagnostic method. *Journal of Autism and Developmental Disorders*, **35**(6), 807-819.

At the present time there are a large number of adults who have suspected Asperger syndrome (AS). In this paper we describe a new instrument, the Adult Asperger Assessment (AAA), developed in our clinic for adults with AS. The need for a new instrument relevant to the diagnosis of AS in adulthood arises because existing instruments are designed for use with children. Properties of the AAA include (1) being electronic, data-based, and computer-scorable; (2) linking with two screening instruments [the Autism Spectrum Quotient (AQ) and the Empathy Quotient (EQ)]; and (3) employing a more stringent set of diagnostic criteria than DSM-IV, in order to avoid false

positives. The AAA is described, and its use with a series of $n = 42$ clinic-patients is reported. Thirty-seven of these (88%) met DSM-IV criteria, but only 34 of these (80%) met AAA criteria. The AAA is therefore more conservative than DSM-IV.

Bartlett, C. W., Gharani, N., Millonig, J. H., & Brzustowicz, L. M. (2005). Three autism candidate genes: a synthesis of human genetic analysis with other disciplines. *International Journal of Developmental Neuroscience*, 23(2-3), 221-234.

Autism is a particularly complex disorder when considered from virtually any methodological framework, including the perspective of human genetics. We first present a review of the genetic analysis principles relevant for discussing autism genetics research. From this body of work we highlight results from three candidate genes, REELIN (RELN), SEROTONIN TRANSPORTER (5HTT), and ENGRAILED 2 (EN2) and discuss the relevant neuroscience, molecular genetics, and statistical results that suggest involvement of these genes in autism susceptibility. As will be shown, the statistical results from genetic analysis, when considered alone, are in apparent conflict across research groups. We use these three candidate genes to illustrate different problems in synthesizing results from non-overlapping research groups examining the same problem. However, when basic genetic principles and results from other scientific disciplines are incorporated into a unified theoretical framework, at least some of the difficulties with interpreting results can be understood and potentially overcome as more data becomes available to the field of autism research. Integrating results from several scientific frameworks provides new hypotheses and alternative data collection strategies for future work.

Bartlett, C. W., Goedken, R., & Vieland, V. J. (2005). Effects of updating linkage evidence across subsets of data: Reanalysis of the autism genetic resource exchange data set. *American Journal of Human Genetics*, 76(4), 688-695.

Results of autism linkage studies have been difficult to interpret across research groups, prompting the use of ever-increasing sample sizes to increase power. However, increasing sample size by pooling disparate collections for a single analysis may, in fact, not increase power in the face of genetic heterogeneity. Here, we applied the posterior probability of linkage (PPL), a method designed specifically to analyze multiple heterogeneous data sets, to the Autism Genetic Resource Exchange collection of families by analyzing six clinically defined subsets of the data and updating the PPL sequentially over the subsets. Our results indicate a substantial probability of linkage to chromosome 1, which had been previously overlooked; our findings also provide a further characterization of the possible parent-of-origin effects at the 17q11 locus that were previously described in this sample. This analysis illustrates that the way in which heterogeneity is addressed in linkage analysis can dramatically affect the overall conclusions of a linkage study.

Beglinger, L. and T. Smith (2005). "Concurrent validity of social subtype and IQ after early intensive behavioral intervention in children with autism: A preliminary investigation." *Journal of Autism and Developmental Disorders* 35(3): 295-303.

Three subtypes of autism based on social style have been proposed by Wing: active-but-odd, passive, or aloof. Previous research has shown evidence of an association between IQ and Wing subtype in untreated children and adults. Because IQ changes can accompany behavioral treatment, but often only for a subset of children, social subtype may be related to treatment responsiveness. We administered a social subtyping measure, the Wing Subgroups Questionnaire (WSQ), at various points in treatment to younger children than previously studied with autism in early, intensive behavioral intervention (EIBI). Thirty-seven children in EIBI (aged 39-71 months, amount of EIBI 0-44 months) were assessed to determine whether Wing's three proposed subtypes were found in this sample and whether subtypes were associated with current IQ and change in IQ after a period of EIBI. Results confirmed that all three subtypes were present and correlated with IQ after a period of intervention, as well as with change in IQ. Participants classified as aloof had significantly lower IQ scores and changes in IQ after EIBI than other children. Future studies should extend these findings by examining whether social subtype at pretreatment predicts EIBI outcome.

Bernier, R., G. Dawson, et al. (2005). "Individuals with autism spectrum disorder show normal responses to a fear potential startle paradigm." *Journal of Autism and Developmental Disorders* **35**(5): 575-583.

The present study utilized a fear potentiated startle paradigm to examine amygdala function in individuals with autism spectrum disorder. Two competing hypotheses regarding amygdala dysfunction in autism have been proposed: (1) The amygdala is under-responsive, in which case it would be predicted that, in a fear potentiated startle experiment, individuals with autism would exhibit decreased fear conditioning and/or potentiation, and (2) The amygdala is over responsive, in which case an exaggerated potentiation of the startle response would be predicted. Fourteen adolescents and adults diagnosed with autism spectrum disorder and 14 age, gender, IQ, and anxiety level-matched typical adolescents and adults participated. Both participants with autism and typical participants potentiated the startle response following fear conditioning and no group differences in the latency or amplitude of the potentiated startle response were found. These results suggest that this aspect of amygdala function, namely fear conditioning and potentiation of the startle response, is intact in individuals with autism.

Berument, S. K., Starr, E., Pickles, A., Tomlins, M., Papanikolaou, K., Lord, C., et al. (2005). Pre-linguistic autism diagnostic observation schedule adapted for older individuals with severe to profound mental retardation: A pilot study. *Journal of Autism and Developmental Disorders*, *35*(6), 821-829.

The Autism Diagnostic Observational Schedule (ADOS) is a semi-structured observational scale developed to assess social interaction, communication and play in individuals who are suspected to have autism. Since the ADOS is not suitable to be used with severely or profoundly mentally retarded adolescents and adults with very limited language skills, materials and some of the tasks of the PL-ADOS and the original ADOS (the former versions of the current ADOS) were adapted. Results indicated that almost all of the overall ratings showed good reliability and discriminative diagnostic validity. Furthermore, the combination of codings into an overall algorithm score on

social/communicative behavior resulted in a sensitivity of .82 and a specificity of .85 when using a cut-off score of 15.

Bishop, D. V. M., & Norbury, C. F. (2005). Executive functions in children with communication impairments, in relation to autistic symptomatology - I: Generativity. *Autism, 9*(1), 7-27.

Previous research has found that people with autism generate few novel responses in ideational fluency tasks, and it has been suggested this deficit is a specific correlate of stereotyped/repetitive behavior. We assessed generativity in children with pragmatic language impairment (PLI) who showed communicative abnormalities resembling those seen in autism. We compared four groups: high-functioning autism; PLI; specific language impairment; and control. Generativity was measured using two fluency tasks previously shown to be sensitive to autistic disorder. Correlational analysis revealed a significant relationship between the percentage of correct responses on the fluency tasks and measures of communicative abnormality. It is often assumed that pragmatic difficulties are caused by limitations of social cognition. This study suggests that difficulties in generating relevant ideas can be another cause of autistic-like communicative abnormalities.

Bonora, E., Lamb, J. A., Barnby, G., Sykes, N., Moberly, T., Beyer, K. S., et al. (2005). Mutation screening and association analysis of six candidate genes for autism on chromosome 7q. *European Journal of Human Genetics, 13*(2), 198-207.

Genetic studies have provided evidence for an autism susceptibility locus (AUTS1) on chromosome 7q. Screening for mutations in six genes mapping to 7q, CUTL1, SRPK2, SYPL, LAMB1, NRCAM and PTPRZ1 in 48 unrelated individuals with autism led to the identification of several new coding variants in the genes CUTL1, LAMB1 and PTPRZ1. Analysis of genetic variants provided evidence for association with autism for one of the new missense changes identified in LAMB1; this effect was stronger in a subgroup of affected male sibling pair families, implying a possible specific sex-related effect for this variant. Association was also detected for several polymorphisms in the promoter and untranslated region of NRCAM, suggesting that alterations in expression of this gene may be linked to autism susceptibility.

Cardy, J. E. O., Flagg, E. J., Roberts, W., Brian, J., & Roberts, T. P. L. (2005). Magnetoencephalography identifies rapid temporal processing deficit in autism and language impairment. *Neuroreport, 16*(4), 329-332.

Deficient rapid temporal processing may contribute to impaired language development by interfering with the processing of brief acoustic transitions crucial for speech perception. Using magnetoencephalography, evoked neural activity (M50, M100) to two 40 ms tones passively presented in rapid succession was recorded in 10 neurologically normal adults and 40 8-17-year-olds with autism, specific language impairment, Asperger syndrome or typical development. While 80% of study participants with intact language (Asperger syndrome, typical development, adults) showed identifiable responses to the second tone, which presented rapid temporal processing demands, 65% of study participants with impaired language (autism, specific language

impairment) did not, despite having shown identifiable responses to the first tone. Rapid temporal processing impairments may be fundamentally associated with impairments in language rather than autism spectrum disorder.

Cardy, J. E. O., Flagg, E. J., Roberts, W., & Roberts, T. P. L. (2005). Delayed mismatch field for speech and non-speech sounds in children with autism. *Neuroreport*, *16*(5), 521-525.

This study investigated the magnetic mismatch field elicited by changes in streams of vowels or spectrally matched tones in children with autism spectrum disorder (ASD) relative to children with typical development to explore whether impaired sound discrimination may contribute to language impairments in autism spectrum disorder. Using magnetoencephalography, we recorded evoked neural activity to 300-Hz and 700-Hz tones (and /u/ and /a/ vowels) presented in an oddball paradigm with deviant stimuli (15%) occurring within a train of standards (85%). The magnetic mismatch field was robustly observed in both groups, but children with autism spectrum disorder demonstrated a significantly delayed magnetic mismatch field compared with typically developing peers. Difficulty parsing transient differences in sounds may lead to impaired acoustic or phonological representations and subsequent language impairment in autism spectrum disorder.

Carper, R. A., & Courchesne, E. (2005). Localized Enlargement of the Frontal Cortex in Early Autism. *Biological Psychiatry*, *57*(2), 126-133.

Background: Evidence from behavioral, imaging, and postmortem studies indicates that the frontal lobe, as well as other brain regions such as the cerebellum and limbic system, develops abnormally in children with autism. It is not yet clear to what extent the frontal lobe is affected; that is, whether all regions of frontal cortex show the same signs of structural maldevelopment. Methods: In the present study, we measured conical volume in four subregions of the frontal cortex in 2-year-old to 9-year-old boys with autism and normal control boys. Results: The dorsolateral region showed a reduced age effect in patients when compared with control subjects, with a predicted 10% increase in volume from 2 years of age to 9 years of age compared with a predicted 48% increase for control subjects. In a separate analysis, dorsolateral and medial frontal regions were significantly enlarged in patients aged 2 to 5 years compared with control subjects of the same age, but the precentral gyrus and orbital cortex were not. Conclusions: These data indicate regional variation in the degree of frontocortical overgrowth with a possible bias toward later developing or association areas. Possible mechanisms for these regional differences are discussed.

Chakrabarti, S., & Fombonne, E. (2005). Pervasive developmental disorders in preschool children: Confirmation of high prevalence. *American Journal of Psychiatry*, *162*(6), 1133-1141.

Objective: The rate of reported pervasive developmental disorders has increased, and the authors found a rate of 62.6 per 10,000 in a previous study of preschoolers in Stafford, U. K. They conducted another survey in 2002 to estimate the prevalence in children in a later birth cohort and to compare it to previous findings from the same area. Method: Screening for developmental problems included 10,903 children ages 4.0 to 6.0 years

who were living in a Midlands town on the survey date. Children with symptoms suggestive of pervasive developmental disorders were intensively assessed by a multidisciplinary team using standardized diagnostic interviews, psychometric tests, and medical workups. Results: Sixty-four children (85.9% boys) were diagnosed with pervasive developmental disorders. The prevalence was 58.7 per 10,000, with a 95% confidence interval (CI) of 45.2-74.9, for all pervasive developmental disorders, 22.0 per 10,000 (95% CI = 14.1-32.7) for autistic disorder, and 36.7 per 10,000 (95% CI = 26.2-49.9) for other variants. These rates were not significantly different from the previous rates. The mean age at diagnosis was 37.8 months, and 53.1% of the children were originally referred by health visitors. Of the 64 children with pervasive developmental disorders, 29.8% had mental retardation, but this rate varied by disorder subtype. Few children had associated medical conditions. Conclusions: The rate of pervasive developmental disorders is higher than reported 15 years ago. The rate in this study is comparable to that in previous birth cohorts from the same area and surveyed with the same methods, suggesting a stable incidence.

Chakrabarti, S., C. Haubus, et al. (2005). "A model of early detection and diagnosis of autism spectrum disorder in young children." *Infants and Young Children* **18**(3): 200-211.

Autism and autism spectrum disorder (ASD) are a group of severe developmental disorders that are characterized by 3 core sets of developmental abnormalities: impairment of social interaction, verbal and nonverbal communication, and restricted, repetitive patterns of behavior. The disorder is far more common than previously thought. There is no cure for autism but it is apparent that early detection followed by early intervention is likely to provide the best chance of long-term beneficial outcome in this condition. Unfortunately, until recently, there had been no validated method of comprehensive early detection of ASD, nor a tool with adequate sensitivity and specificity to be recommended for universal screening of preschool children with ASD. We describe a model of comprehensive early detection and diagnosis of ASD that is achieved by using the resources of primary care workers and a multidisciplinary team with skill and experience in assessing developmental problems in young children and specific expertise in ASD. Both early detection and diagnosis may be carried out by this team in collaboration with parents and primary care professionals and can result in high rates of detection and diagnosis of ASD.

Charman, T., Taylor, E., Drew, A., Cockerill, H., Brown, J. A., & Baird, G. (2005). Outcome at 7 years of children diagnosed with autism at age 2: predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. *Journal of Child Psychology and Psychiatry*, *46*(5).

Objective: To examine the predictive validity of symptom severity, cognitive and language measures taken at ages 2 and 3 years to outcome at age 7 in a sample of children diagnosed with autism at age 2.

Method: Twenty-six children diagnosed with autism at age 2 were re-assessed at ages 3 and 7 years. At each age symptom severity, cognitive and language assessments were completed.

Results: The pattern of autistic symptom severity varied over time by domain. Across time, children moved across diagnostic boundaries both in terms of clinical diagnosis and in terms of instrument diagnosis on the Autism Diagnostic Interview-Revised (ADI-R). On all measures group variability in scores increased with age. Although non-verbal IQ (NVIQ) for the group as a whole was stable across the 3 assessments, this masked considerable individual instability. Standard assessments at age 2 did not predict outcome at age 7 even within the same domain of functioning. In contrast, standard assessments at age 3 did predict outcome. However, a measure of rate of non-verbal communicative acts taken from an interactive play-based assessment at age 2 was significantly associated with language, communication and social outcomes at age 7.

Conclusions: The trajectory of autism symptoms over time differed in different domains, suggesting that they may be, at least in part, separable. Variability in language, NVIQ and symptom severity increased over time. Caution is required when interpreting the findings from assessments of children with autism at age 2 years. At this age measures of rate of non-verbal communication might be more informative than scores on standard psychometric tests. Predictive validity of assessments at age 3 years was greater.

Cohen, D., Pichard, N., Tordjman, S., Baumann, C., Burglen, L., Excoffier, E., et al. (2005). Specific genetic disorders and autism: Clinical contribution towards their identification. *Journal of Autism and Developmental Disorders*, 35(1), 103-116.

Autism is a heterogeneous disorder that can reveal a specific genetic disease. This paper describes several genetic diseases consistently associated with autism (fragile X, tuberous sclerosis, Angelman syndrome, duplication of 15q11-q13, Down syndrome, San Filippo syndrome, MECP2 related disorders, phenylketonuria, Smith-Magenis syndrome, 22q13 deletion, adenylosuccinate lyase deficiency, Cohen syndrome, and Smith-Lemli-Opitz syndrome) and proposes a consensual and economic diagnostic strategy to help practitioners to identify them. A rigorous initial clinical screening is presented to avoid unnecessary laboratory and imaging studies. Regarding psychiatric nosography, the concept of "syndromal autism"-autism associated with other clinical signs-should be promoted because it may help to distinguish patients who warrant a multidisciplinary approach and further investigation.

Corsello, C. M. (2005). Early intervention in autism. *Infants and Young Children*, 18(2), 74-85.

We now know that professionals can diagnose children with autism when they are as young as 2 years of age (Lord, 1995). Screening and the role of the pediatrician have become even more critical as we have recognized the stability of early diagnosis over time and the importance of early intervention. At this point, experts working with children with autism agree that early intervention is critical. There is professional consensus about certain crucial aspects of treatment (intensity, family involvement, focus on generalization) and empirical evidence for certain intervention strategies. However, there are many programs developed for children with autism that differ in philosophy and a lack of research comparing the various intervention programs. Most of the programs for children with autism that exist are designed for children of preschool age, and not all are widely known or available. While outcome data are published for some of these programs, empirical studies comparing intervention programs are lacking. In this review,

existing intervention programs and empirical studies on these programs will be reviewed, with a particular emphasis on the birth to 3 age group.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., et al. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, 8(4), 519-526.

Diminished gaze fixation is one of the core features of autism and has been proposed to be associated with abnormalities in the neural circuitry of affect. We tested this hypothesis in two separate studies using eye tracking while measuring functional brain activity during facial discrimination tasks in individuals with autism and in typically developing individuals. Activation in the fusiform gyrus and amygdala was strongly and positively correlated with the time spent fixating the eyes in the autistic group in both studies, suggesting that diminished gaze fixation may account for the fusiform hypoactivation to faces commonly reported in autism. In addition, variation in eye fixation within autistic individuals was strongly and positively associated with amygdala activation across both studies, suggesting a heightened emotional response associated with gaze fixation in autism.

Dawson, G., S. J. Webb, et al. (2005). "Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism." *Development and Psychopathology* 17(3): 679-697.

Neuroimaging and behavioral studies have shown that children and adults with autism have impaired face recognition. Individuals with autism also exhibit atypical event-related brain potentials to faces, characterized by a failure to show a negative component (N170) latency advantage to face compared to nonface stimuli and a bilateral, rather than right lateralized, pattern of N170 distribution. In this report, performance by 143 parents of children with autism on standardized verbal, visual-spatial, and face recognition tasks was examined. It was found that parents of children with autism exhibited a significant decrement in face recognition ability relative to their verbal and visual spatial abilities. Event-related brain potentials to face and nonface stimuli were examined in 21 parents of children with autism and 21 control adults. Parents of children with autism showed an atypical event-related potential response to faces, which mirrored the pattern shown by children and adults with autism. These results raise the possibility that face processing might be a functional trait marker of genetic susceptibility to autism. Discussion focuses on hypotheses regarding the neurodevelopmental and genetic basis of altered face processing in autism. A general model of the normal emergence of social brain circuitry in the first year of life is proposed, followed by a discussion of how the trajectory of normal development of social brain circuitry, including cortical specialization for face processing, is altered in individuals with autism. The hypothesis that genetic-mediated dysfunction of the dopamine reward system, especially its functioning in social contexts, might account for altered face processing in individuals with autism and their relatives is discussed.

de Bildt, A., Kraijer, D., Sytema, S., & Minderaa, R. (2005). The psychometric properties of the Vineland Adaptive Behavior Scales in children and adolescents with mental retardation. *Journal of Autism and Developmental Disorders*, 35(1), 53-62.

The psychometric properties of the Vineland Adaptive Behavior Scales Survey Form were studied in a total population of children and adolescents with MR, and in the specific levels of functioning (n = 826, age 4-18 years). The original division into (sub)domains, as assigned by the authors, was replicated in the total population and in the mild and moderate levels of functioning. In the severe and profound levels of functioning the structure was less well recognized. The reliability of the instrument proved to be good in the total population and the subgroups. The construct validity was high in all groups. The implications of these findings are discussed with respect to the usefulness of the Vineland for the population with MR.

de Bildt, A., Sytema, S., Kraijer, D., & Minderaa, R. (2005). Prevalence of pervasive developmental disorders in children and adolescents with mental retardation. *Journal of Child Psychology and Psychiatry*, 46(3), 275-286.

Background: Insight into the prevalence of pervasive developmental disorder (PDD) in children and adolescents with mental retardation (MR) is known to be of clinical importance. However, estimating this prevalence is complicated. The literature reports prevalence rates ranging from 3% through 50%. This variation seems to be related to the concepts of PDD under study, the instruments used, and the studied populations. The present study aimed to estimate a reliable prevalence rate of PDD. Methods: A total population-based screening with the PDD-MRS and the ABC (n = 825) was followed by further assessment of children and adolescents at high risk for PDD according to these instruments, and for controls, with the ADI-R, ADDS-G and a DSM-IV-TR classification (n = 188). Results: The instruments lead to different prevalence rates that range from 7.8% to 19.8%. The differences in the estimated prevalence rates are related to the concept of PDD and the instruments they represent. The DSM-IV-TR prevalence (16.7%) seems to be the most reliable and well-founded estimate, since this prevalence rate is based on information from multiple informants and multiple time periods. Conclusions: The reported prevalence rates provide policy makers with an up-to-date and more substantiated guideline for the allocation of resources for children and adolescents with MR and PDD. The height of the prevalence should alert professionals that PDD is widespread in the population with MR. Keywords: Prevalence, PDD, MR

Dementieva, Y. A., Vance, D. D., Donnelly, S. L., Elston, L. A., Wolpert, C. M., Ravan, S. A., et al. (2005). Accelerated head growth in early development of individuals with autism. *Pediatric Neurology*, 32(2), 102-108.

Macrocephaly is one of the most consistent physical findings reported in autistic individuals. Previous studies attempted to determine if macrocephaly is associated with risk for autism. This study hypothesizes that an abnormal acceleration in head growth during early development, rather than macrocephaly, is associated with autism risk. To investigate this hypothesis, head circumference data were examined in 251 individuals from 82 multiplex (at least two individuals with autism) and 113 sporadic (no family history) families with autism. This examination included longitudinal measurements for 79 individuals. Nineteen percent of the original 251 individuals were found to have

macrocephaly (head circumference >97%). Abnormal acceleration in head growth was defined as an increase of 25 or more percentile points in head circumference between two consecutive measurements. Thirty-five percent of individuals with multiple head circumference records had an abnormal increase in head circumference. Furthermore, autistic individuals with accelerated head growth in early childhood displayed higher levels of adaptive functioning and less social impairment. This study confirms the presence of abnormal acceleration in head growth during the first and second months of life in a subgroup of autistic individuals.

Dumont-Mathieu, T. and D. Fein (2005). "Screening for autism in young children: The modified checklist for autism in toddlers (M-CHAT) and other measures." Mental Retardation and Developmental Disabilities Research Reviews **11**(3): 253-262.

The literature on the importance of early identification and early intervention for children with developmental disabilities such as autism continues to grow. The increased prevalence of autistic spectrum disorders has fostered research efforts on the development and validation of autism-specific screening instruments for use with young children. There are currently several such autism-specific screening tools meant to be used with young children in various stages of development. Data from a few of these screening instruments have been published, and they include the Checklist for Autism in Toddlers (CHAT), Pervasive Developmental Disorders Screening Test (PDDST), Screening Tool for Autism in Two year olds (STAT), Checklist for Autism in Toddlers-23 (CHAT-23), and the Modified Checklist for Autism in Toddlers (M-CHAT). In this review, these five tools designed for use with children under three years old will be highlighted. In particular, the Modified Checklist for Autism in Toddlers (M-CHAT) will be discussed. (c) 2005 Wiley-Liss, Inc.

Farmer, M. and A. Oliver (2005). "Assesment of pragmatic difficulties and socio-emotional adjustment in practice." International Journal of Language & Communication Disorders **40**(4): 403-429.

Background: In professional practice, psychologists and other professionals such as therapists and teachers receive referrals of many children who present with social, emotional and behavioural difficulties that are difficult to understand and assess. The problems of some of these children may stem from pragmatic difficulties in communication. This paper reports the results of a study on the use of checklists in professional practice to assist in the identification of these difficulties. Aims: (1) To ascertain whether two checklists, Bishop's (1998) Children's Communication Checklist and Goodman's (1997) Strengths and Difficulties Questionnaire, would discriminate between groups of children diagnosed as having autism, autistic spectrum disorder/Asperger's syndrome, pragmatic difficulties and children with other types of specific language impairment. (2) To investigate whether specific aspects of pragmatic difficulties can be identified as relating to difficulties in peer relationships. (3) To investigate whether ratings of pragmatic difficulties are related solely to difficulties in

social relations or whether other aspects of socio-emotional adjustment are also affected. Methods & Procedures: The Children's Communication Checklist and the Strengths and Difficulties Questionnaire were completed by the teachers and other professionals working with a sample of children (n=38) with a range of types of communication difficulty and being educated in schools run by one English Local Education Authority. Outcomes & Results: Analyses of variance indicated that the scores for pragmatic competence and socio-emotional adjustment difficulties were useful in discriminating between groups of children with diagnoses of autism or autistic spectrum disorder, Asperger's syndrome, and other types of language impairment. No specific pragmatic correlates of social interactional difficulties were found, but ratings of hyperactivity were significantly correlated with pragmatic difficulties. Conclusions: The two checklists if used together provide useful information on the profiles of strengths and weaknesses of children with a range of communication and or emotional/behavioural difficulties. The use of both checklists in this study demonstrated the differential profiles of pragmatic competence and socio-emotional adjustment of children with different types of communication difficulty.

Fine, S. E., A. Weissman, et al. (2005). "Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome." Journal of Autism and Developmental Disorders **35**(4): 461-470.

In this study, we assessed the presence of autism spectrum disorders (ASD) among children with a confirmed 22q11.2 deletion (n = 98). The children's caregivers completed screening measures of ASD behaviors, and for those whose scores indicated significant levels of these behaviors, a standardized diagnostic interview (Autism Diagnostic Interview-Revised; ADI-R) was administered. Results demonstrated that over 20% of children (n = 22) were exhibiting significant levels of autism spectrum symptoms based on the screening measures. Based upon the ADI-R, 14 children qualified for a diagnosis of an ASD, and for 11 of those children a diagnosis of autism was most appropriate. These findings increase our knowledge of developmental disorders associated with the 22q11.2 deletion and point to avenues for future investigation.

Fombonne, E. (2005). Epidemiology of autistic disorder and other pervasive developmental disorders. *Journal of Clinical Psychiatry*, *66*, 3-8.

Is the incidence of autistic disorder and other pervasive developmental disorders (PDDs) increasing? Recent epidemiological surveys of autistic disorder and other PDDs have heightened awareness of and concern about the prevalence of these disorders; however, differences in survey methodology, particularly changes in case definition and case identification over time, have made comparisons between surveys difficult to perform and interpret. Recent surveys suggest that the rate of all PDDs is about 60 per 10,000. The prevalence of autism today is estimated at 13 per 10,000, Asperger's disorder is approximately 3 per 10,000, and childhood disintegrative disorder is very rare at about 0.2 per 10,000. The assessment process, sample size, publication year, and geographic location of studies all have an effect on prevalence estimates. In addition, data from many of these surveys indicate correlates of autistic disorder and other PDDs with IQ, gender, and other medical disorders.

Fombonne, E. (2005). "The changing epidemiology of autism." *Journal of Applied Research in Intellectual Disabilities* **18**(4): 281-294.

This article reviews epidemiological studies of autism and related disorders. Study designs and sample characteristics are summarized. Currently, conservative prevalence estimates are: 13/10000 for autistic disorder, 21/10000 for pervasive developmental disorders not otherwise specified, 2.6/10000 for Asperger disorder, and 2/100000 for childhood disintegrative disorder. Newer surveys suggest that the best estimate for the prevalence of all autistic spectrum disorders is close to 0.6%. A detailed analysis of time trends in rates of pervasive developmental disorders is then provided. It is concluded that most of the increase is accounted for by changes in diagnostic concepts and criteria, and by improved identification. Whether or not there is, in addition to these factors, a true increase in the incidence of the disorder cannot be examined from available data.

Geurts, H. M., Verte, S., Oosterlaan, J., Roeyers, H., & Sergeant, J. A. (2005). ADHD subtypes: do they differ in their executive functioning profile? *Archives of Clinical Neuropsychology*, *20*(4), 457-477.

Asperger syndrome (AS) is a childhood-onset disorder often described as a mild variant of autism. Although classified as a distinct disorder in the DSM-IV, its overlap with autism continues to be a matter of ongoing debate. While the family genetic origins of autism are well established, few studies have investigated this topic in AS using current operational criteria. In this report, we examined the family psychiatric history of 58 subjects with AS diagnosed according to DSM-IV criteria (48 males; mean age 13.34; mean full scale IQ 104.87). All subjects had a history of mild autistic social deficits; focused special interests; normal level of intelligence; and an odd and often pedantic manner of speaking. None had a previous diagnosis of autism. Of the 58 subjects with Asperger syndrome, three had first degree relatives with AS; nine (15%) had a family history of schizophrenia; and 35 (60%) had a family history of depression. Of the 64 siblings, four had a diagnosis of AS and none of autism. Compared with a group of 39 subjects with normal intelligence autism (high functioning autism, HFA; 33 males; mean age 15.34; mean full scale IQ 85.89) subjects with AS were more likely to have relatives with depression; schizophrenia; and the broader autistic phenotype. Possible reasons for and implications of these findings are discussed.

Gray, K. M., & Tonge, B. J. (2005). Screening for autism in infants and preschool children with developmental delay. *Australian and New Zealand Journal of Psychiatry*, *39*(5).

This study aimed to identify emotional and behavioural problems specific to young children with autism using the Developmental Behaviour Checklist (DBC-P) and thus evaluate the efficacy of this checklist as a screening tool for autism in children with developmental delay aged 18-48 months. Method: Subjects were 60 children with autism and developmental delay and 60 children with developmental delay without autism. Results: Features were identified which differentiated the children with autism from those with developmental delay without autism. Analyses revealed that a 17-item version of the DBC-P performed well as a screening tool for autism, with an 'area under the curve' of 0.874, sensitivity of 0.8750, and specificity of 0.6909. Conclusions: The DBC-P offers a

potential simple and inexpensive method of screening at risk populations of preschool children with developmental delay for autism, thus facilitating timely referral to scarce specialist autism diagnostic services.

Hale, C. M. and H. Tager-Flusberg (2005). "Brief report: The relationship between discourse deficits and autism symptomatology." Journal of Autism and Developmental Disorders **35**(4): 519-524.

This study investigated the relationship between discourse deficits to a broader range of other symptoms in 57 children with autism. We hypothesized that autism symptomatology, as measured by the Autism Diagnostic Observation Schedule (ADOS), would be related to the children's difficulty in maintaining an ongoing topic of discourse. Children provided a natural language sample while interacting with one parent. These language samples were coded for the child's use of off-topic or noncontingent utterances. Results showed significant relationships between overall diagnostic symptomatology, and more specifically, deficits in communication as measured by the ADOS-G, and noncontingent discourse. The findings provide diagnostic validity to the ADOS-G and highlight in greater detail the significant communication impairment in autism.

Hale, C. M., & Tager-Flusberg, H. (2005). Social communication in children with autism - The relationship between theory of mind and discourse development. *Autism*, *9*(2), 157-178.

This longitudinal study investigated the developmental trajectory of discourse skills and theory of mind in 57 children with autism. Children were tested at two time points spaced 1 year apart. Each year they provided a natural language sample while interacting with one parent, and were given standardized vocabulary measures and theory of mind a developmentally sequenced battery of tasks. The language samples were coded for conversational skills, specifically the child's use of topic-related contingent utterances. Children with autism made significant gains over 1 year in the ability to maintain a topic of discourse. Hierarchical regression analyses demonstrated that theory of mind skills contributed unique variance to individual differences in contingent discourse ability and vice versa, when measured concurrently; however, they did not predict longitudinal changes. The findings offer some empirical support for the hypothesis that theory of mind is linked to communicative competence in children with autism.

Handen, B. L., & Hofkosh, D. (2005). Secretin in children with autistic disorder: A double-blind, placebo-controlled trial. *Journal of Developmental and Physical Disabilities*, *17*(2), 95-106.

A number of recent studies have examined the efficacy of secretin (a polypeptide neurotransmitter) to treat symptoms associated with autism. Initial anecdotal reports indicated significant gains in social relatedness and language. However, recent double-blind studies have documented few significant differences between placebo and active medication. We report the results of a double-blind, placebo-controlled, crossover study of the efficacy of secretin in eight children with autism. No group differences between placebo and secretin were found on measures of behavior and core features of autism. Parents reported anecdotal improvement in communication and social relatedness, but

such gains tended to occur during both placebo and active medication conditions. However, a single subject did experience improvement in the core features of autism and behavior for a 3-4-week period following the secretin infusion. The results add further research support of the lack of clinical efficacy of this medication in the treatment of autism.

Hastings, R. P., H. Kovshoff, et al. (2005). "Systems analysis of stress and positive perceptions in mothers and fathers of pre-school children with autism." Journal of Autism and Developmental Disorders **35**(5): 635-644.

Systemic analyses of psychological functioning in families of children with autism have typically shown that parents report different experiences (e.g., stress) and that siblings may also be affected. The purpose of the present research was more explicitly to address relationships between child, partner, and parent variables. Parents of 48 children with autism (41 mother-father pairs) reported on child characteristics, and their own stress and mental health. Mothers were found to report both more depression and more positive perceptions than fathers. Regression analyses revealed that paternal stress and positive perceptions were predicted by maternal depression; maternal stress was predicted by their children's behavior problems (not adaptive behavior or autism symptoms) and by their partner's depression. The future testing of the mechanisms underlying these results is discussed. In addition, the need is emphasized for more systemic analyses to understand the psychological functioning of children with autism and their siblings and parents.

Hefter, R. L., D. S. Manoach, et al. (2005). "Perception of facial expression and facial identity in subjects with social developmental disorders." Neurology **65**(10): 1620-1625.

Background: It has been hypothesized that the social dysfunction in social developmental disorders (SDDs), such as autism, Asperger disorder, and the socioemotional processing disorder, impairs the acquisition of normal face-processing skills. The authors investigated whether this purported perceptual deficit was generalized to both facial expression and facial identity or whether these different types of facial perception were dissociated in SDDs. Methods: They studied 26 adults with a variety of SDD diagnoses, assessing their ability to discriminate famous from anonymous faces, their perception of emotional expression from facial and nonfacial cues, and the relationship between these abilities. They also compared the performance of two defined subgroups of subjects with SDDs on expression analysis: one with normal and one with impaired recognition of facial identity. Results: While perception of facial expression was related to the perception of nonfacial expression, the perception of facial identity was not related to either facial or nonfacial expression. Likewise, subjects with SDDs with impaired facial identity processing perceived facial expression as well as those with normal facial identity processing. Conclusion: The processing of facial identity and that of facial expression are dissociable in social developmental disorders. Deficits in perceiving facial expression may be related to emotional processing more than face processing. Dissociations between the perception of facial identity and facial emotion are consistent with current cognitive models of face processing. The results argue against

hypotheses that the social dysfunction in social developmental disorder causes a generalized failure to acquire face-processing skills.

Hellings, J. A., Nickel, E. J., Weckbaugh, M., McCarter, K., Mosier, M., & Schroeder, S. R. (2005). The overt aggression scale for rating aggression in outpatient youth with autistic disorder: Preliminary findings. *Journal of Neuropsychiatry and Clinical Neurosciences*, 17(1), 29-35.

Aggression is a common and costly problem in youth with developmental disabilities. Rating scales that accurately capture and measure subtypes of aggression phenomenology, frequency and severity are urgently needed, in both clinical practice and research. The authors studied the Overt Aggression Scale (OAS) in a preliminary sample of eight outpatients who participated in an ongoing placebo-controlled study of valproate for aggression in autism. Subjects' OAS aggression scores showed significant correlation with the already validated retrospectively rated Aberrant Behavior Checklist Community Scale irritability subscale. Further study of the OAS in outpatients with aggression and developmental disabilities is warranted.

Hollander, E., E. Anagnostou, et al. (2005). "Striatal volume on magnetic resonance imaging and repetitive behaviors in autism." *Biological Psychiatry* 58(3): 226-232.

Background: The repetitive behaviors seen in autism phenotypically resemble those seen in obsessive-compulsive disorder (OCD) and Tourette Syndrome (TS), disorders in which structural and functional abnormalities of the basal ganglia (BG) are present and correspond to the severity of repetitive behaviors. Methods: Seventeen subjects with autism by DSM-IV and Autism Diagnostic Interview (ADI) and 17 matched controls completed a 1.5 T magnetic resonance image (MRI) of the brain. Two blinded researchers, with good inter-rater reliability, outlined the right and left caudate and putamen. Autistic and control BG volumes covaried for total brain volume were compared using analysis of covariance. BG volumes within the autistic group were correlated with the ADI Repetitive Behavior scores (ADI-C domain). Results: Right caudate volume controlled for total brain volume was significantly larger in autistic subjects than in controls. In addition, right caudate and total putamen volumes correlated positively with repetitive behavior scores on the ADI-C domain, particularly the higher order OCD-like repetitive behaviors. Conclusions: Increased right caudate volume in autism is of interest, since this has also been observed in OCD patients. Increased volume of the right caudate and total putamen positively correlated with greater repetitive behaviors, supporting the hypothesis of BG dysfunction associated with repetitive behaviors in autistic adults.

Howlin, P., Alcock, J., & Burkin, C. (2005). An 8 year follow-up of a specialist supported employment service for high-ability adults with autism or Asperger syndrome. *Autism*, 9(5), 533-549.

Few supported employment programmes have been specifically designed for people with autism, especially those who are more able. This study examines the outcome of a supported employment service (NAS Prospects) for adults with autism or Asperger syndrome (IQ 60+) over an 8 year period. Approximately 68 percent of clients

found employment. Of the 192 jobs, the majority were permanent contracts and most involved administrative, technical or computing work. Assessment of current clients indicates that IQ, language skills and educational attainments are high. However, work has also been found for those of lower abilities. Individuals supported by Prospects show a rise in salaries, contribute more tax and claim fewer benefits. Satisfaction with the scheme is high among clients, employers and support workers. Although the programme continues to incur a financial deficit, this has decreased. Moreover, there are many non-financial benefits, which are difficult to quantify. The importance of specialist employment support of this kind is discussed.

Howlin, P., Karpf, J., & Turk, J. (2005). Behavioural characteristics and autistic features in individuals with Cohen Syndrome. *European Child & Adolescent Psychiatry*, *14*(2), 57-64.

Diagnostic criteria for Cohen Syndrome are based largely on physical characteristics, and systematic information about behaviour and social functioning is limited. Typically, individuals with this condition are described as being very sociable and as showing low rates of pathology. However, recent studies have indicated that behavioural difficulties may occur more frequently than previously suggested and that autistic features may be relatively common. The present investigation of 45 individuals with Cohen Syndrome (age 4-48 years) found that, although 57% of the sample were reported as showing some behavioural disturbance, problems related mainly to anxiety and social interactions; marked anti-social behaviours were rare. Twenty-two individuals met criteria for autism on standardised diagnostic assessments, although the "autistic profile" was somewhat atypical. The implications of these findings for our understanding of Cohen Syndrome are discussed.

Hrdlicka, M., I. Dudova, et al. (2005). "Subtypes of autism by cluster analysis based on structural MRI data." *European Child & Adolescent Psychiatry* **14**(3): 138-144.

The aim of our study was to subcategorize Autistic Spectrum Disorders (ASD) using a multidisciplinary approach. Sixty four autistic patients (mean age 9.4 +/- 5.6 years) were entered into a cluster analysis. The clustering analysis was based on MRI data. The clusters obtained did not differ significantly in the overall severity of autistic symptomatology as measured by the total score on the Childhood Autism Rating Scale (CARS). The clusters could be characterized as showing significant differences: Cluster 1: showed the largest sizes of the genu and splenium of the corpus callosum (CC), the lowest pregnancy order and the lowest frequency of facial dysmorphic features. Cluster 2: showed the largest sizes of the amygdala and hippocampus (HPC), the least abnormal visual response on the CARS, the lowest frequency of epilepsy and the least frequent abnormal psychomotor development during the first year of life. Cluster 3: showed the largest sizes of the caput of the nucleus caudatus (NC), the smallest sizes of the HPC and facial dysmorphic features were always present. Cluster 4: showed the smallest sizes of the genu and splenium of the CC, as well as the amygdala, and caput of the NC, the most abnormal visual response on the CARS, the highest frequency of epilepsy, the highest pregnancy order, abnormal psychomotor development during the first year of life was always present and facial dysmorphic features were always present. This multidisciplinary approach seems to be a promising method for subtyping autism.

Joseph, R. M., S. D. Steele, et al. (2005). "Self-ordered pointing in children with autism: failure to use verbal mediation in the service of working memory?" *Neuropsychologia* 43(10): 1400-1411.

This study tested the hypothesis that children with autism are impaired in using verbal encoding and rehearsal strategies in the service of working memory. Participants were 24 high-ability, school-age children with autism and a comparison group matched on verbal and non-verbal IQ, receptive and expressive vocabulary, and visual memory. Working memory was assessed using verbal and non-verbal variants of a nonspatial, self-ordered pointing test in which children had to point to a new stimulus in a set upon each presentation without repeating a previous choice. In the verbal condition, the stimuli were pictures of concrete, nameable objects, whereas in the non-verbal condition, the stimuli were not easily named or verbally encoded. Participants were also administered a verbal span task to assess non-executive verbal rehearsal skills. Although the two groups were equivalent in verbal rehearsal skills, the autism group performed significantly less well in the verbal, but not the non-verbal, self-ordered pointing test. These findings suggested that children with autism are deficient in the use of verbal mediation strategies to maintain and monitor goal-related information in working memory. The findings are discussed in terms of possible autistic impairments in episodic memory as well as working memory. (c) 2005 Elsevier Ltd. All rights reserved.

Joseph, R. M., McGrath, L. M., & Tager-Flusberg, H. (2005). Executive dysfunction and its relation to language ability in verbal school-age children with autism. *Developmental Neuropsychology*, 27(3), 361-378.

This study examined executive dysfunction and its relation to language ability in verbal school-age children with autism. Participants were 37 children with autism and 31 nonautistic comparison participants who were matched on age and on verbal and nonverbal IQ but not on language ability, which was lower in the autism group. Children with autism exhibited deficits compared to the comparison group across all 3 domains of executive function that were assessed including working memory (Block Span Backward; Isaacs & Vargha-Khadem, 1989), working memory and inhibitory control (NEPSY Knock-Tap; Korkman, Kirk, & Kemp, 1998), and planning (NEPSY Tower; Korkman et al., 1998). Children with autism were less developed than the comparison group in their language skills, but correlational analyses revealed no specific association between language ability and executive performance in the autism group. In contrast, executive performance was positively correlated with language ability in the comparison group. This pattern of findings suggest that executive dysfunction in autism is not directly related to language impairment per se but rather involves an executive failure to use of language for self-regulation.

Kaland, N., Moller-Nielsen, A., Smith, L., Mortensen, E. L., Callesen, K., & Gottlieb, D. (2005). The Strange Stories test - A replication study of children and adolescents with Asperger syndrome. *European Child & Adolescent Psychiatry*, 14(2), 73-82.

The aim of the present study was to assess the ability of 21 children and adolescents with Asperger syndrome (AS) of normal intelligence to infer mental states in a Story context using Happe's [15] Strange Stories test. The participants in the AS group were compared with an age-matched control group (N = 20) of normally developing children and adolescents on a test of social understanding. The test material comprised social communication such as Pretence, joke, Lie, White Lie, Figure of Speech, Misunderstanding, Persuasion, irony, Double Bluff and Contrary Emotions, Appearance/Reality and Forgetting. As compared to the controls, the participants in the AS group performed less well on these tasks, and answered fewer correct mental state inferences, but performed well on a physical state control task. This study supports the main finding of earlier studies, showing that even individuals with AS of normal intelligence have problems in using mental state terms context-appropriately when tested on the Strange Stories test.

Kamp-Becker, I., Matzejat, F., Wolf-Ostermann, K., & Remschmidt, H. (2005). The Marburg Rating Scale for Aspergers syndrome (MBAS) - a screening instrument for high functioning autistic disorders. *Zeitschrift Fur Kinder-Und Jugendpsychiatrie Und Psychotherapie*, 33(1), 15-26.

Objectives: Asperger's Syndrome is a disorder of uncertain nosological validity, which is difficult to differentiate from high-functioning autism. Even today these disorders are unfortunately diagnosed very late, often in the wake of earlier, different diagnoses. The purpose of this study is to present a screening instrument (MBAS), which is sensitive to these disorders.**Methods:** The instrument was tested among a total of 91 probands (44 of whom had been diagnosed as autistic, and 47 of whom had been diagnosed with a non-autistic disorder).**Results:** The items on the WAS were of average difficulty; generally, the all item-total correlation was good. The total scale has an internal consistency of Cronbach's alpha = .91 and the convergent validity of the WAS and the ADI-R reached $r = .61$ ($p = .001$). The total score of the questionnaire discriminated highly significantly between the group with autism and that without. At a sensitivity of 95.5% and a specificity of 95.7% the number! of misclassifications is low. False negative classifications occurred only in the case of very young children.**Conclusions:** The MBAS is a reliable and valid instrument for screening and generating tentative diagnoses of high-functioning autism. The questionnaire is well suited for the selection and generation of tentative diagnoses of autism on a high-functioning level.

Klin, A., Pauls, D., Schultz, R., & Volkmar, F. (2005). Three diagnostic approaches to Asperger syndrome: Implications for research. *Journal of Autism and Developmental Disorders*, 35(2), 221-234.

Objective: To examine the implications for research of the use of three alternative definitions for Asperger syndrome (AS). Differences across the three nosologic systems were examined in terms of diagnostic assignment, IQ profiles, comorbid symptoms, and familial aggregation of social and other psychiatric symptoms. **Method:** Standard data on diagnosis, intellectual functioning, comorbidity patterns, and family history were obtained on 65 individuals screened for a very high probability of having autism without mental retardation (or higher functioning autism, HFA) or AS. Diagnoses of AS were

established based on three different approaches: DSM-IV, presence/absence of communicative phrase speech by 3 years, and a system designed to highlight prototypical features of AS. Results: Agreement between the three diagnostic systems was poor. AS could be differentiated from HFA (but not from PDD-NOS) on the basis of IQ profiles in two of the three systems. Differences in patterns of comorbid symptomatology were obtained in two of the three systems, although differences were primarily driven by the PDD-NOS category. Only one of the approaches yielded differences relative to aggregation of the broader phenotype in family members. Conclusions: Diagnostic assignments of AS based on three commonly used approaches have low agreement and lead to different results in comparisons of IQ profiles, patterns of comorbidity, and familial aggregation of psychiatric symptoms across the approach-specific resultant groups of HFA, AS, and PDD-NOS.

Koshino, H., Carpenter, P. A., Minshew, N., Cherkassky, V. L., Keller, T. A., & Just, M. A. (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage*, 24(3), 810-821.

An fMRI study was used to measure the brain activation of a group of adults with high-functioning autism compared to a Full Scale and Verbal IQ and age-matched control group during an n-back working memory task with letters. The behavioral results showed comparable performance, but the fMRI results suggested that the normal controls might use verbal codes to perform the task, while the adults with autism might use visual codes. The control group demonstrated more activation in the left than the right parietal regions, whereas the autism group showed more right lateralized activation in the prefrontal and parietal regions. The autism group also had more activation than the control group in the posterior regions including inferior temporal and occipital regions. The analysis of functional connectivity yielded similar patterns for the two groups with different hemispheric correlations. The temporal profile of the activity in the prefrontal regions was more correlated with the left parietal regions for the control group, whereas it was more correlated with the right parietal regions for the autism group.

Kraijer, D. and A. de Bildt (2005). "The PDD-MRS: An instrument for identification of autism spectrum disorders in persons with mental retardation." *Journal of Autism and Developmental Disorders* 35(4): 499-513.

The Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS) is described. The PDD-MRS is a simple classification and screening instrument devised for identification of autistic disorders (of the entire spectrum) in persons with mental retardation from mild to profound levels, age-range 2-55 years. The norms of the scale are based on the research protocols of 1230 Dutch persons with mental retardation. The scale's sensitivity for the entire normative sample was found to be 92.4%; calculated separately for persons at all levels of mentally retarded functioning, male and female persons, speaking and non-speaking persons and five age categories, the sensitivity figures range between 87.0 and 100.0%. The specificity of the scale is also 92.4%; for the aforementioned subgroups separately, the specificity figures range between 84.6 and 95.5%. Roughly similar values for sensitivity and specificity were

found when using the scale with severely visually impaired/blind persons; severely hearing-impaired/deaf persons; persons with Down syndrome; male persons with fragile X syndrome. The original version of the PDD-MRS dates from 1990; since then the scale has been widely used in the Netherlands and Belgium. The PDD-MRS should be regarded as a useful instrument for identifying PDD in persons with mental retardation.

Kuhl, P. K., Coffey-Corina, S., Padden, D., & Dawson, G. (2005). Links between social and linguistic processing of speech in preschool children with autism: behavioral and electrophysiological measures. *Developmental Science*, 8(1), F1-F12

Data on typically developing children suggest a link between social interaction and language learning, a finding of interest both to theories of language and theories of autism. In this study, we examined social and linguistic processing of speech in preschool children with autism spectrum disorder (ASD) and typically developing chronologically matched (TDCA) and mental age matched (TDMA) children. The social measure was an auditory preference test that pitted 'motherese' speech samples against non-speech analogs of the same signals. The linguistic measure was phonetic discrimination assessed with mismatch negativity (MMN), an event-related potential (ERP). As a group, children with ASD differed from controls by: (a) demonstrating a preference for the non-speech analog signals, and (b) failing to show a significant MMN in response to a syllable change. When ASD children were divided into subgroups based on auditory preference, and the ERP data reanalyzed, ASD children who preferred non-speech still failed to show an MMN whereas ASD children who preferred motherese did not differ from the controls. The data support the hypothesis of an association between social and linguistic processing in children with ASD.

Lamb, J. A., Barnby, G., Bonora, E., Sykes, N., Bacchelli, E., Blasi, F., et al. (2005). Analysis of IMGSAC autism susceptibility loci: evidence for sex limited and parent of origin specific effects. *Journal of Medical Genetics*, 42(2), 132-137.

Background and methods: Autism is a severe neurodevelopmental disorder, which has a complex genetic predisposition. The ratio of males to females affected by autism is approximately 4: 1, suggesting that sex specific factors are involved in its development. We reported previously the results of a genomewide screen for autism susceptibility loci in 83 affected sibling pairs (ASP), and follow up analysis in 152 ASP. Here, we report analysis of an expanded sample of 219 ASP, using sex and parent of origin linkage modelling at loci on chromosomes 2, 7, 9, 15, and 16. Results: The results suggest that linkage to chromosomes 7q and 16p is contributed largely by the male male ASP (MLS = 2.55 \pm 0.12, and MLS = 2.48 \pm 0.00, for the 145 male - male and 74 male - female/ female - female ASP on chromosomes 7 and 16 respectively). Conversely linkage to chromosome 15q appears to be attributable to the male - female/ female - female ASP (MLS = 2.62 \pm 0.00, for non-male and male - male ASP respectively). On chromosomes 2 and 9, all ASP contribute to linkage. These data, supported by permutation, suggest a possible sex limited effect of susceptibility loci on chromosomes 7, 15, and 16. Parent of origin linkage modelling indicates two distinct regions of paternal and maternal identity by descent sharing on chromosome 7 (paternal MLS = 1.46 at similar to 112 cM, and maternal MLS = 1.83 at similar to 135 cM; corresponding maternal and paternal MLS = 0.53 and 0.28 respectively), and maternal specific sharing on chromosome 9 (maternal

MLS = 1.99 at,30 cM; paternal MLS = 0.02). Conclusion: These data support the possibility of two discrete loci underlying linkage of autism to chromosome 7, and implicate possible parent of origin specific effects in the aetiology of autism.

Landa, R. J. and M. C. Goldberg (2005). "Language, social, and executive functions in high functioning autism: A continuum of performance." Journal of Autism and Developmental Disorders **35**(5): 557-573.

This study examined language and executive functions (EF) in high-functioning school-aged individuals with autism and individually matched controls. Relationships between executive, language, and social functioning were also examined. Participants with autism exhibited difficulty on measures of expressive grammar, figurative language, planning, and spatial working memory. A mixed profile of impaired and enhanced abilities was noted in set-shifting. While controls showed the typical increase in errors when shifting sets from an intra-dimensional to an extra-dimensional stimulus, this pattern was not noted in participants with autism. Relationships between EF, language, and social performance were weak to nonexistent. Implications for theories of core deficit in autism and dissociable nature of the language and executive impairments in autism are discussed.

Lecavalier, L. (2005). An evaluation of the Gilliam Autism Rating Scale. *Journal of Autism and Developmental Disorders*, 35(6), 795-805.

The Gilliam Autism Rating Scale was developed to identify individuals with autism in research and clinical settings. It has benefited from wide use and acceptance but has received little empirical attention. The purpose of this study was to evaluate the construct and diagnostic validity, interrater reliability, and effects of participant characteristics of the GARS in a large and heterogeneous sample of children and adolescents with autism spectrum disorders. 360 parent and teacher ratings were submitted to factor analysis. A three-factor solution explaining 38% of the variance was obtained. Almost half of all items loaded on a Repetitive and Stereotyped Behavior factor. The Developmental Disturbance subscale did not contribute to the Autism Quotient (AQ) and was poorly related to other subscales. Internal consistency for the three behavioral subscales was good but low for the Developmental Disturbance subscale. The average AQ was significantly lower than what was reported in the test manual, suggesting low sensitivity with the current cutoff criteria. Interrater reliability was also much lower than originally reported by the instrument's developer. No significant age or gender effects were found. Level of impairment, as measured by adaptive behavior, was negatively related to total and subscale scores. The implications of these findings were discussed, as was the use of diagnostic instruments in the field in general.

Lopez, B. R., A. J. Lincoln, et al. (2005). "Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder." Journal of Autism and Developmental Disorders **35**(4): 445-460.

The executive function theory was utilized to examine the relationship between cognitive process and the restricted, repetitive symptoms of Autistic Disorder (AD). Seventeen adults with AD were compared to 17 nonautistic controls on a new executive

function battery (Delis-Kaplin Executive Function Scales). Restricted, repetitive symptoms were measured by a variety of instruments (i.e., the Autism Diagnostic Observation Schedule, Autism Diagnostic Interview-Revised, Gilliam Autism Rating Scale, and the Aberrant Behavior Checklist). The study replicated the executive function profile that has been reported in adults with AD. In addition to the replication findings, the study found several executive processes (i.e., cognitive flexibility, working memory, and response inhibition) were highly related to the restrictive, repetitive symptoms of AD; whereas, other executive process (i.e., planning and fluency) were not found to be significantly correlated with restricted, repetitive symptoms. Similarly, we found an executive function model consisting of relative strengths and deficits was the best predictor of restricted, repetitive symptoms of autism. The implications for the executive function theory and how the theory predicts core symptoms of autism are discussed.

Luyster, R., Richler, J., Risi, S., Hsu, W. L., Dawson, G., Bernier, R., et al. (2005). Early regression in social communication in autism spectrum disorders: A CPEA study. *Developmental Neuropsychology*, 27(3), 311-336.

In a multisite study of 351 children with autism spectrum disorders, 21 children with developmental delays, and 31 children with typical development, this study used caregiver interviews (i.e., the Autism Diagnostic Interview Revised) at the time of entry into other research projects and follow-up telephone interviews designed for this project to describe the children's early acquisition and loss of social-communication milestones. Children who had used words spontaneously and meaningfully and then stopped talking were described by their caregivers as showing more gestures, greater participation in social games, and better receptive language before the loss and fewer of these skills after the loss than other children with autism spectrum disorders. A significant minority of children with autism without word loss showed a very similar pattern of loss of social-communication skills, a pattern not observed in the children with developmental delays or typical development.

Ma, D. Q., Jaworski, J., Menold, M. M., Donnelly, S., Abramson, R. K., Wright, H. H., et al. (2005). Ordered-subset analysis of savant skills in autism for 15q11-q13. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, 135B(1).

Autism is a complex disorder characterized by genetic and phenotypic heterogeneity. Analysis of phenotypically homogeneous subtypes has been used to both confirm and narrow potential autism linkage regions such as the chromosomal region 15q11-q13. Increased evidence for linkage in this region had been found in a subgroup of 21 autism families (total families = 94) stratified based on a savant skill factor (SSF) from the Autism Diagnostic Interview, Revised (ADI-R). We examined the savant phenotypic finding in our sample of 91 multiplex autism families. Using two-point parametric analysis in stratification with a cutoff point of a savant skill score of 0.16, our families failed to demonstrate linkage to 15q11-q13. In addition, ordered subset analysis (OSA) using SSF as a covariate also failed to show evidence for linkage. Our findings do not support savant skills as an informative phenotypic subset for linkage in our sample.

McAlonan, G. M., Cheung, V., Cheung, C., Suckling, J., Lam, G. Y., Tai, K. S., et al. (2005). Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. *BRAIN*(128), 268-276.

Autism is a disorder of neurodevelopment resulting in pervasive abnormalities in social interaction and communication, repetitive behaviours and restricted interests. There is evidence for functional abnormalities and metabolic dysconnectivity in 'social brain' circuitry in this condition, but its structural basis has proved difficult to establish reliably. Explanations for this include replication difficulties inherent in 'region of interest' approaches usually adopted, and variable inclusion criteria for subjects across the autism spectrum. Moreover, despite a consensus that autism probably affects widely distributed brain regions, the issue of anatomical connectivity has received little attention. Therefore, we planned a fully automated voxel-based whole brain volumetric analysis in children with autism and normal IQ. We predicted that brain structural changes would be similar to those previously shown in adults with autism spectrum disorder and that a correlation analysis would suggest structural dysconnectivity. We included 17 stringently diagnosed children with autism and 17 age-matched controls. All children had IQ >80. Using Brain Activation and Morphological Mapping (BAMM) software, we measured global brain and tissue class volumes and mapped regional grey and white matter differences across the whole brain. With the expectation that volumes of interconnected regions correlate positively, we carried out a preliminary exploration of 'connectivity' in autism by comparing the nature of inter-regional grey matter volume correlations with control. Children with autism had a significant reduction in total grey matter volume and significant increase in CSF volume. They had significant localized grey matter reductions within fronto-striatal and parietal networks similar to findings in our previous study, and additional decreases in ventral and superior temporal grey matter. White matter was reduced in the cerebellum, left internal capsule and fornices. Correlation analysis revealed significantly more numerous and more positive grey matter volumetric correlations in controls compared with children with autism. Thus, using similar diagnostic criteria and image analysis methods in otherwise healthy populations with an autistic spectrum disorder from different countries, cultures and age groups, we report a number of consistent findings. Taken together, our data suggest abnormalities in the anatomy and connectivity of limbic-striatal 'social' brain systems which may contribute to the brain metabolic differences and behavioural phenotype in autism.

McConachie, H., Le Couteur, A., & Honey, E. (2005). Can a diagnosis of Asperger syndrome be made in very young children with suspected autism spectrum disorder? *Journal of Autism and Developmental Disorders*, 35(2), 167-176.

Of a cohort of 104 children with Autism, PDD-NOS or specific language disorder, recruited at age 2–3 years of age, only three appeared to meet diagnostic assessment criteria for Asperger syndrome (AS). The children were followed up at 4–5 years, and assessments at both time points included the Autism Diagnostic Interview (ADI-R), the Autism Diagnostic Observation Schedule (ADOS) and the Mullen Scales of Early Learning. The paper explores the reasons why so few children with possible AS were identified early, including problems inherent in the assessment tools and the range of normal variation within characteristics required for a diagnosis. Only 10 children altogether had first words by 24 months, and abilities in the average range, and 9 were

followed up. All of these able children had varied repetitive behaviours, and these increased in terms of ADI-R algorithm score over a 13 month interval. However, items concerning resistance to change and liking of routines tended to decrease in terms of reported impact on the child and family. Repetitive behaviours seem significant in the early referral of able children for a PDD diagnosis, but identification of children with AS is more likely to occur reliably once children are older and enter school.

McCracken, J. T. (2005). "Risperidone treatment of autistic disorder: Longer-term benefits and blinded discontinuation after 6 months." *American Journal of Psychiatry* **162**(7): 1361-1369.

Objective: Risperidone is effective for short-term treatment of aggression, temper outbursts, and self-injurious behavior in children with autism. Because these behaviors may be chronic, there is a need to establish the efficacy and safety of longer-term treatment with this agent. Method: The authors conducted a multisite, two-part study of risperidone in children ages 5 to 17 years with autism accompanied by severe tantrums, aggression, and/or self-injurious behavior who showed a positive response in an earlier 8-week trial. Part I consisted of 4-month open-label treatment with risperidone, starting at the established optimal dose; part II was an 8-week randomized, double-blind, placebo-substitution study of risperidone withdrawal. Primary outcome measures were the Aberrant Behavior Checklist irritability subscale and the Clinical Global Impression improvement scale. Results: Part I included 63 children. The mean risperidone dose was 1.96 mg/day at entry and remained stable over 16 weeks of open treatment. The change on the Aberrant Behavior Checklist irritability subscale was small and clinically insignificant. Reasons for discontinuation of part I included loss of efficacy (N = 5) and adverse effects (N = 1). The subjects gained an average of 5.1 kg. Part II included 32 patients. The relapse rates were 62.5% for gradual placebo substitution and 12.5% for continued risperidone; this difference was statistically significant. Conclusions: Risperidone showed persistent efficacy and good tolerability for intermediate-length treatment of children with autism characterized by tantrums, aggression, and/or self-injurious behavior. Discontinuation after 6 months was associated with a rapid return of disruptive and aggressive behavior in most subjects.

McGovern, C. W., & Sigman, M. (2005). Continuity and change from early childhood to adolescence in autism. *Journal of Child Psychology and Psychiatry*, *46*(4), 401-408.

Background: This longitudinal study of 48 children diagnosed with autism at 2-5 years of age was designed to test the hypothesis that diagnosis would remain stable for most of the sample but that there would be improvements in symptom severity, adaptive behavior, and emotional responsiveness in adolescence. Methods: A sample of children with autism assessed in both early and middle childhood were observed in late adolescence with the Autism Diagnostic Observation Scale (ADOS) and their parents were administered the Autism Diagnostic Interview-Revised (ADI-R) and the Vineland Adaptive Behavior Scale. Results: All but 2 adolescents (46 of 48) met lifetime criteria for autism according to the ADI-R, and all but 4 adolescents (40 of 44) met criteria for autism spectrum disorder on the ADOS. In contrast to the continuity in diagnosis, parents described improvements in social interactions, repetitive/stereotyped behaviors, adaptive behaviors, and emotional responsiveness to others' distress in adolescence compared to

middle childhood. High-functioning adolescents with autism showed more improvement in these domains than low-functioning adolescents with autism. The extent to which the adolescents were observed to be socially engaged with their peers in school in middle childhood predicted adaptive behavior skills even when intelligence level was statistically constrained. Conclusions: The developmental trajectory of children with autism appears to show both continuity and change. In this sample, most individuals continued to be diagnosed in the autism spectrum but parents reported improvements in adolescence. The results suggest that social involvement with peers improves adaptive behavior skills, and this argues for focusing intervention programs in this area. In addition, it is clear that high-functioning adolescents improve more than low-functioning individuals not only in cognitive abilities but also in social interaction skills. Thus, any early intervention that impacts the cognitive abilities of young children with autism is likely to have a parallel influence on their social skills as they mature into late adolescence and early adulthood.

Meresse, I. G., M. Zilbovicius, et al. (2005). "Autism severity and temporal lobe functional abnormalities." *Annals of Neurology* **58**(3): 466-469.

Two independent studies (1,2) have described bilateral temporal hypoperfusion in autistic children. Temporal regions are implicated in social perception, language, and "theory-of-mind" abilities that are impaired in autism. We investigated a putative relationship between cerebral blood flow (rCBF) measured at rest and clinical profile of 45 autistic children (Autism Diagnostic Interview-Revised [ADI-R] scores). A whole-brain covariance analysis was performed. Significant negative correlation was observed between rCBF and ADI-R score in the left superior temporal gyrus. The more severe the autistic syndrome, the more rCBF is low in this region, suggesting that left superior temporal hypoperfusion is related to autistic behavior severity.

Miles, J. H., Takahashi, T. N., Bagby, S., Sahota, P. K., Vaslow, D. F., Wang, C. H., et al. (2005). Essential versus complex autism: Definition of fundamental prognostic subtypes. *American Journal of Medical Genetics Part A*, *135A*(2), 171-180. Heterogeneity within the autism diagnosis obscures the genetic basis of the disorder and impedes our ability to develop effective treatments. We found that by using two readily available tests, autism can be divided into two subgroups, "essential autism" and "complex autism," with different outcomes and recurrence risks. Complex autism consists of individuals in whom there is evidence of some abnormality of early morphogenesis, manifested by either significant dysmorphology or microcephaly. The remainder have "essential autism." From 1995 to 2001, 260 individuals who met DSM-IV criteria for autistic disorder were examined. Five percent (13/260) were microcephalic and 16% (41/260) had significant physical anomalies. Individually, each trait predicted a poorer outcome. Together they define the "complex autism" subgroup, comprising 20% (46/233) of the total autism population. Individuals with complex autism have lower IQs ($P=0.006$), more seizures ($P=0.0008$), more abnormal EEGs (46% vs. 30%), more brain abnormalities by MRI (28% vs. 13%). Everyone with an identifiable syndrome was in the complex group. Essential autism defines the more heritable group with higher sib recurrence (4% vs. 0%), more relatives with autism (20% vs. 9%), and higher male to female ratio (6.5:1 vs. 3.2:1). Their outcome was better with higher IQs ($P=0.02$) and

fewer seizures ($P=0.0008$). They were more apt to develop autism with a regressive onset (43% vs. 23%, $P=0.02$). Analysis of the features predictive of poor outcome (IQ<55, functionally non-verbal) showed that microcephaly was 100% specific but only 14% sensitive; the presence of physical anomalies was 86% specific and 34% sensitive. The two tests combined yielded 87% specificity, 47% sensitivity, and an odds ratio of 4.8:1 for poor outcome. Separating essential from complex autism should be the first diagnostic step for children with autism spectrum disorders as it allows better prognostication and counseling. Definition of more homogeneous populations should increase power of research analyses.

Milner, K. M., E. E. Craig, et al. (2005). "Prader-Willi syndrome: intellectual abilities and behavioural features by genetic subtype." Journal of Child Psychology and Psychiatry **46**(10): 1089-1096.

Background: Studies of chromosome 15 abnormality have implicated over-expression of paternally imprinted genes in the 15q11-13 region in the aetiology of autism. To test this hypothesis we compared individuals with Prader-Willi syndrome (PWS) due to uniparental disomy (UPD - where paternally imprinted genes are over-expressed) to individuals with the 15q11-13 deletion form of the syndrome (where paternally imprinted genes are not over-expressed). We also tested reports that PWS cases due to the larger type I (TI) form of deletion show differences to cases with the smaller type II (TII) deletion. Method: Ninety-six individuals with PWS were recruited from genetic centres and the PWS association. Forty-nine individuals were confirmed as having maternal UPD of chromosome 15 and were age and sex matched to 47 individuals with a deletion involving 15q11-13 (32 had the shorter (T II) deletion, and 14 had the longer (TI) deletion). Behavioural assessments were carried out blind to genetic status, using the Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview (ADI),the Autism Screening Questionnaire (ASQ), the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS),the Vineland Adaptive Behaviour Scales (VABS), and measurements of intellectual ability, including the Wechsler and Mullen Scales and Raven's Matrices. Results: UPD cases exhibited significantly more autistic-like impairments in reciprocal social interaction on questionnaire, interview and standardised observational measures. Comparison of TI and TII deletion cases revealed few differences, but ability levels tended to be lower in the TI deletion cases. Conclusions: Findings from a large study comparing deletion and UPD forms of Prader-Willi syndrome were consistent with other evidence in indicating that paternally imprinted genes in the 15q11-13 region constitute a genetic risk factor for aspects of autistic symptomatology. These genes may therefore play a role in the aetiology of autism. By contrast with another report, there was no clear-cut relationship between the size of the deletion and the form of cognitive and behavioural phenotype.

Minschew, N. J., Turner, C. A., & Goldstein, G. (2005). The application of short forms of the Wechsler intelligence scales in adults and children with high functioning autism. *Journal of Autism and Developmental Disorders*, *35*(1), 45-52.

We evaluated the predictive accuracy of short forms of the Wechsler intelligence scales for individuals with high functioning autism. Several short forms were derived

from participants who had received the full procedure. Stepwise multiple regression analyses were performed to determine the strength of association between the subtests included in the short form and IQ scores based upon the full test. These analyses were performed for all participants, and also for autism participants with atypical subtest profiles. In all analyses the percentages of explained variance were typically in the .8-9 range. It was concluded that short forms may be used with good predictive accuracy in individuals with high functioning autism, even when the subtest profile is atypical.

Mulder, E. J., Anderson, G. M., Kema, I. P., Brugman, A. M., Ketelaars, C. E. J., de Bildt, A., et al. (2005). Serotonin transporter intron 2 polymorphism associated with rigid-compulsive behaviors in Dutch individuals with pervasive developmental disorder. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, 133B(1), 93-96.

Two putatively functional polymorphisms of the serotonin transporter gene (HTT, SLC6A4) were examined for associations with risk for pervasive developmental disorders (PDDs) and specific autism phenotypes. Dutch patients diagnosed with PDD (N = 125, age range 5-20 years, DSM-IV-TR based criteria, ADI-R and ADOS behavioral assessments) and their parents (N = 230) were genotyped for promoter ins/del (5-HTTLPR) and intron 2 variable number of tandem repeats (VNTR) alleles. Using the transmission disequilibrium test (TDT), no disorder-specific preferential transmission of promoter (long and short) or intron 2 (10- and 12-repeat) alleles was observed. However, multivariate analysis of continuous autism-related behavioral measures revealed that subjects with intron 2 12/12 genotype were significantly more impaired in the rigid-compulsive domain (P = 0.008). Quantitative TDT (QTDT) analysis also showed significant association of the intron 2 VNTR 12-repeat allele with rigid-compulsive behavior (P = 0.015). These results suggest that intron 2 VNTR alleles or nearby polymorphisms in linkage disequilibrium may play a role in specific aspects of the behavioral phenotype of autism.

Norbury, C. F. (2005). "The relationship between theory of mind and metaphor: Evidence from children with language impairment and autistic spectrum disorder." British Journal of Developmental Psychology 23: 383-399.

Happe (1993) proposed that theory of mind (ToM) understanding was necessary for comprehension of metaphorical expressions. The current study investigated the role of both ToM and language ability in metaphor understanding. Ninety-four children aged 8-15 years with communication impairments were grouped according to language ability and autistic symptomatology in the first instance, and then according to ToM performance. Their performance on a metaphor task was compared to 34 typically developing age-matched peers. These analyses showed that only children with language impairment, with or without concurrent autistic features, were impaired on the metaphor task. Furthermore, possession of first-order ToM skills did not ensure metaphor comprehension. Instead, semantic ability was a stronger predictor of performance on the metaphor task. These results are considered with reference to the view that ToM understanding is necessary for the comprehension of metaphor.

Odell, D., Maciulis, A., Cutler, A., Warren, L., McMahon, W. M., Coon, H., et al. (2005). Confirmation of the association of the C4B null allele in autism. *Human Immunology*, 66(2), 140-145.

The objective of this Study was to examine and attempt to confirm our previous findings of an increased frequency of the C4B null allele (C4BQ0) in subjects with autism. Newly identified subjects from Utah and Oregon were Studied. Families evaluated included 85 who had a child with autism and 69 control families. Of the subjects with autism studied, 42.4% carried at least one C4BQ0, compared with 14.5% of the control subjects ($p = 0.00013$), with a relative risk of 4.33. Over half of the C4B null alleles in the subjects with autism involved C4A duplications. A marked increase in the ancestral haplotype 44.1 that lacks a C4B gene and has 2 C4A genes was also observed. The results of this study suggest that the human leukocyte antigen class III C4BQ0 significantly increases the risk for autism. (C) American Society for Histocompatibility and Immunogenetics, 2005. Published by Elsevier Inc.

Oliveira, G., Diogo, L., Grazina, M., Garcia, P., Ataide, A., Marques, C., et al. (2005). Mitochondrial dysfunction in autism spectrum disorders: a population-based study. *Developmental Medicine and Child Neurology*, 47(3), 185-189.

A minority of cases of autism has been associated with several different organic conditions, including bioenergetic metabolism deficiency. In a population-based study, we screened associated medical conditions in a group of 120 children with autism (current age range 11y 5mo to 14y 4mo, mean age 12y 11mo [SD 9.6mo], male:female ratio 2.9:1). Children were diagnosed using Diagnostic and Statistical Manual of Mental Disorders criteria, the Autism Diagnostic Interview--Revised, and the Childhood Autism Rating Scale; 76% were diagnosed with typical autism and 24% with atypical autism. Cognitive functional level was assessed with the Griffiths scale and the Wechsler Intelligence Scale for Children and was in the normal range in 17%. Epilepsy was present in 19 patients. Plasma lactate levels were measured in 69 patients, and in 14 we found hyperlactacidemia. Five of 11 patients studied were classified with definite mitochondrial respiratory chain disorder, suggesting that this might be one of the most common disorders associated with autism (5 of 69; 7.2%) and warranting further investigation.

Owley, T., Walton, L., Salt, J., Guter, S. J., Winnega, M., Leventhal, B. L., et al. (2005). An open-label trial of escitalopram in pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(4), 343-348.

Objective: To assess the effect of escitalopram in the treatment of pervasive developmental disorders (PDDs). Method: This 10-week study had a forced titration, open-label design. Twenty-eight subjects (mean age 125.1 +/- 33.5 months) with a PDD received escitalopram at a dose that increased weekly to a maximum dose of 20 mg as tolerated. The Aberrant Behavior Checklist-Community Version (ABC-CV) and the Clinical Global Impression scale (CGI) were used to assess outcome. Results: There was significant improvement in ABC-CV Irritability Subscale Scores (baseline mean 20.5 +/- 5.9 to final mean 10.9 +/- 7.2; $p <= .001$) and in the other ABC-CV Subscales. Improvement on Clinical Global Improvement Scale severity rating was also significant (baseline mean 5.2 +/- 1.0 to final mean 4.6 +/- 1.2; $p <= .001$). Twenty-five percent of the subjects responded at a dose less than 10 mg and did not tolerate the 10-mg dose, and

an additional 36% responded at a dose greater than or equal to 10 mg. Final dose was unrelated to weight and only weakly correlated with age. Conclusions: This open-label study found escitalopram to be useful in treating some difficulties common in PDDs. A wide variability in dose was found that could not be accounted for by weight and only partially by age. The study provides information useful for the design of double-blind, placebo-controlled studies of escitalopram in PDDs.

Ozonoff, S., Williams, B. J., & Landa, R. (2005). Parental report of the early development of children with regressive autism - The delays-plus-regression phenotype. *Autism, 9*(5), 461-486.

Most children with autism demonstrate developmental abnormalities in their first year, whereas others display regression after mostly normal development. Few studies have examined the early development of the latter group. This study developed a retrospective measure, the Early Development Questionnaire (EDQ), to collect specific, parent-reported information about development in the first 18 months. Based on their EDQ scores, 60 children with autism between the ages of 3 and 9 were divided into three groups: an early onset group (n = 29), a definite regression group (n = 23), and a heterogeneous mixed group (n = 8). Significant differences in early social development were found between the early onset and regression groups. However, over 50 percent of the children who experienced a regression demonstrated some early social deficits during the first year of life, long before regression and the apparent onset of autism. This group, tentatively labeled 'delays-plus-regression', deserves further study.

Paul, R., Augustyn, A., Klin, A., & Volkmar, F. R. (2005). Perception and production of prosody by speakers with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 35*(2), 205-220.

Speakers with autism spectrum disorders (ASD) show difficulties in suprasegmental aspects of speech production, or prosody, those aspects of speech that accompany words and sentences and create what is commonly called "tone of voice." However, little is known about the perception of prosody, or about the specific aspects of prosodic production that result in the perception of "oddness." The present study examined the perception and production of a range of specific prosodic elements in an experimental protocol involving natural speech among speakers with ASD between 14 and 21 years of age, in comparison with a typical control group. Results revealed ceiling effects limiting interpretation of findings for some aspects of prosody. However, there were significant between-group differences in aspects of stress perception and production. The implications of these findings for understanding prosodic deficits in speakers with autism spectrum disorders, and for future research in this area, are discussed.

Philippi, A., E. Roschmann, et al. (2005). "Haplotypes in the gene encoding protein kinase c-beta (PRKCB1) on chromosome 16 are associated with autism." *Molecular Psychiatry* **10**(10): 950-960.

Autism is a developmental disorder characterized by impairments in social interaction and communication associated with repetitive patterns of interest or behavior. Autism is highly influenced by genetic factors. Genome-wide linkage and candidate gene

association approaches have been used to try and identify autism genes. A few loci have repeatedly been reported linked to autism. Several groups reported evidence for linkage to a region on chromosome 16p. We have applied a direct physical identity-by-descent (IBD) mapping approach to perform a high-density (0.85 megabases) genome-wide linkage scan in 116 families from the AGRE collection. Our results confirm linkage to a region on chromosome 16p with autism. High-resolution single-nucleotide polymorphism (SNP) genotyping and analysis of this region show that haplotypes in the protein kinase c-beta gene are strongly associated with autism. An independent replication of the association in a second set of 167 trio families with autism confirmed our initial findings. Overall, our data provide evidence that the PRKCB1 gene on chromosome 16p may be involved in the etiology of autism.

Pry, R., Petersen, A., & Baghdadli, A. (2005). The relationship between expressive language level and psychological development in children with autism 5 years of age. *Autism, 9*(2), 179-189.

The age of detection of autism varies and may be linked to differences in the severity of disturbance and any associated retardation. Symptom intensity, overall language level, age of recognition of first disturbances and level of psychological development were examined in 222 children with pervasive developmental disorder with a mean age of 5 years. Results showed a positive correlation between language level and psychological development as well as between language level and intensity of symptoms. The central position of language in psychological development is discussed.

Rice, S. A., Bigler, E. D., Cleavinger, H. B., Tate, D. F., Sayer, J., McMahon, W., et al. (2005). Macrocephaly, corpus callosum morphology, and autism. *Journal of Child Neurology, 20*(1), 34-41.

Although the cause of autism is undetermined, a general consensus has been that some type of early aberrant neural development underlies the disorder. Given the increased prevalence of macrocephaly in autism, one theory of abnormal neural development implicates early brain growth resulting in larger brain and head size in autism. Surface area measurements of the midsagittal section of the corpus callosum can be used as an index of neural development and white-matter integrity because the corpus callosum is the major white-matter structure that interconnects the two cerebral hemispheres. The purpose of this study was to obtain corpus callosum surface area, shape, and contour in a sample of non-mentally retarded autistic subjects with macrocephaly (n = 12) and compare them with those of matched (n = 8), typically developing control subjects with benign macrocephaly. No significant differences were found in surface area, shape, or contour between groups, nor did corpus callosum surface area relate to measures of IQ or picture vocabulary. These findings suggest no unique difference in overall regional corpus callosum surface area in autism with macrocephaly.

Rogers, S. J. and S. Ozonoff (2005). "Annotation: What do we know about sensory dysfunction in autism? A critical review of the empirical evidence." *Journal of Child Psychology and Psychiatry* **46**(12): 1255-1268.

Background: Unusual responses to sensory stimuli are seen in many children with autism. Their presence was highlighted both in early accounts of autism and in more recent first-person descriptions. There is a widespread belief that sensory symptoms characterize autism and differentiate it from other disorders. This paper examines the empirical evidence for this assumption. Method: All controlled experimental laboratory investigations published since 1960 were identified through systematic searches using Medline/PubMed and PsycInfo search engines. A total of 48 empirical papers and 27 theoretical or conceptual papers were reviewed. Results: Sensory symptoms are more frequent and prominent in children with autism than in typically developing children, but there is not good evidence that these symptoms differentiate autism from other developmental disorders. Certain groups, including children with fragile X syndrome and those who are deaf-blind, appear to demonstrate higher rates of sensory symptoms than children with autism. In reviewing the evidence relevant to two theories of sensory dysfunction in autism, over- and under-arousal theory, we find that there is very little support for hyper-arousal and failure of habituation in autism. There is more evidence that children with autism, as a group, are hypo-responsive to sensory stimuli, but there are also multiple failures to replicate findings and studies that demonstrate lack of group differences. Conclusions: The use of different methods, the study of different sensory modalities, and the changing scientific standards across decades complicate interpretation of this body of work. We close with suggestions for future research in this area.

Rutter, M. (2005). Autism research: Lessons from the past and prospects for the future. *Journal of Autism and Developmental Disorders*, 35(2), 241-257.

The paper uses both the author's experience of research training, and the empirical studies of autism in which he participated over the last 40-plus years, to derive research lessons and to consider the needs and prospects for future research. Attention is drawn to: the importance of mentors; the need to use technologies in a hypothesis-testing fashion; the importance of possible creative/innovative leaps and of recognition of the unexpected; the need to ask challenging questions and to recognize when the original ideas were mistaken. There is great value in broadening the scientific strategies used to investigate a particular condition and much is to be gained by deliberately seeking parallels with other conditions.

Sallows, G. O. and T. D. Graupner (2005). "Intensive behavioral treatment for children with autism: Four-year outcome and predictors." *American Journal on Mental Retardation* 110(6): 417-438.

Twenty-four children with autism were randomly assigned to a clinic-directed group, replicating the parameters of the early intensive behavioral treatment developed at UCLA, or to a parent-directed group that received intensive hours but less supervision by equally well-trained supervisors. Outcome after 4 years of treatment, including cognitive, language, adaptive, social, and academic measures, was similar for both groups. After combining groups, we found that 48% of all children showed rapid learning, achieved average post-treatment scores, and at age 7, were succeeding in regular education classrooms. Treatment outcome was best predicted by pretreatment imitation, language,

and social responsiveness. These results are consistent with those reported by Lovaas and colleagues.

Santangelo, S. L. and K. Tsatsanis (2005). "What is known about autism - Genes, brain, and behavior." *American Journal of Pharmacogenomics* 5(2): 71-92.

Autism is a neurodevelopmental disorder of genetic origins, with a heritability of about 90%. Autistic disorder is classed within the broad domain of pervasive developmental disorders (PDD) that also includes Rett syndrome, childhood disintegrative disorder, Asperger syndrome, and PDD not otherwise specified (PDD-NOS). Prevalence estimates suggest a rate of 0.1-0.2% for autism and 0.6% for the range of PDD disorders. There is considerable phenotypic heterogeneity within this class of disorders as well as continued debate regarding their clinical boundaries. Autism is the prototypical PDD, and is characterized by impairments in three core domains: social interaction, language development, and patterns of behavior (restricted and stereotyped). Clinical pattern and severity of impairment vary along these dimensions, and the level of cognitive functioning of individuals with autism spans the entire range, from profound mental retardation to superior intellect. There is no single biological or clinical marker for autism, nor is it expected that a single gene is responsible for its expression; as many as 15+ genes may be involved. However, environmental influences are also important, as concordance in monozygotic twins is less than 100% and the phenotypic expression of the disorder varies widely, even within monozygotic twins. Multiple susceptibility factors are being explored using varied methodologies, including genome-wide linkage studies, and family- and case-control candidate gene association studies. This paper reviews what is currently known about the genetic and environmental risk factors, neuropathology, and psychopharmacology of autism. Discussion of genetic factors focuses on the findings from linkage and association studies, the results of which have implicated the involvement of nearly every chromosome in the human genome. However, the most consistently replicated linkage findings have been on chromosome 7q, 2q, and 15q. The positive associations from candidate gene studies are largely unreplicated, with the possible exceptions of the GABRB3 and serotonin transporter genes. No single region of the brain or pathophysiological mechanism has yet been identified as being associated with autism. Postmortem findings, animal models, and neuroimaging studies have focused on the cerebellum, frontal cortex, hippocampus, and especially the amygdala. The cerebello-thalamo-cortical circuit may also be influential in autism. There is evidence that overall brain size is increased in some individuals with autism. Presently there are no drugs that produce major improvements in the core social or pragmatic language deficits in autism, although several have limited effects on associated behavioral features. The application of new techniques in autism research is being proposed, including the investigation of abnormal regulation of gene expression, proteomics, and the use of MRI and Postmortem analysis of the brain.

Scahill, L. (2005). Diagnosis and evaluation of pervasive developmental disorders. *Journal of Clinical Psychiatry*, 66, 19-25.

Accurate diagnosis and appropriate treatment of pervasive developmental disorders (PDDs), including autistic disorder, Asperger's disorder, and pervasive

developmental disorder not otherwise specified, are necessary to ensure the best possible outcomes for children with these disorders. In the past, it was not uncommon for children with PDDs to wait several years from the time of parental recognition of developmental delay to the determination of the correct diagnosis and initiation of treatment. Increased awareness of PDDs and the availability of better assessment tools have improved the detection of these conditions in children. A wide variety of standardized diagnostic checklists, interviews, and observational measures are available to assist the clinician in making an accurate PDD diagnosis. A comprehensive evaluation also establishes a baseline of adaptive functioning and problematic behavior, which is essential for subsequent assessment of progress. This article discusses the differential diagnosis and evaluation of PDDs, focusing on the various assessment tools. The elements of a contemporary diagnostic evaluation and behavioral assessment are presented. The application of discretionary evaluations for special situations are also introduced.

Sherer, M. R. and L. Schreibman (2005). "Individual behavioral profiles and predictors of treatment effectiveness for children with autism." Journal of Consulting and Clinical Psychology **73**(3): 525-538.

Differential responsiveness to intervention programs suggests the inadequacy of a single treatment approach for all children with autism. One method for reducing outcome variability is to identify participant characteristics associated with different outcomes for a specific intervention. In this investigation, an analysis of archival data yielded 2 distinct behavioral profiles for responders and nonresponders to a widely used behavioral intervention, pivotal response training (PRT). In a prospective study, these profiles were used to select 6 children (3 predicted responders and 3 predicted nonresponders) who received PRT. Children with pretreatment responder profiles evidenced positive changes on a range of outcome variables. Children with pretreatment nonresponder profiles did not exhibit improvements; These results offer promise for the development of individualized treatment protocols for children with autism.

Sigman, M., & McGovern, C. W. (2005). Improvement in cognitive and language skills from preschool to adolescence in autism. *Journal of Autism and Developmental Disorders*, *35*(1), 15-23.

This paper reports on the developmental progression of a sample of 48 adolescents and young adults with autism who were previously assessed at preschool age and again in the mid-school period. In contrast to the earlier period when about one-third of the children made dramatic gains, cognitive and language skills tended to remain stable or decline over this time span. The gain in mental and language age of the non-retarded adolescents with autism was less than half the change in their chronological age. The mentally retarded adolescents with autism showed some gain in mental age over time but this was far less than their change in chronological age, and they showed almost no gain in language age. Early childhood predictors of language skills in adolescence were functional play skills, responsiveness to others' bids for joint attention, and the frequency of requesting behaviors.

Skuse, D. H., W. P. L. Mandy, et al. (2005). "Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist." *British Journal of Psychiatry* **187**: 568-572.

Background Autistic traits are widely distributed in the general population, but the boundaries of the autistic spectrum are unclear. Whole-population surveys of unselected samples of children are hampered by the lack of appropriate screening instruments. Aims To assess whether the Social and Communication Disorders Checklist (SCDC) fulfils the need for a sensitive measure of autistic traits, which can be completed in a few minutes and which measures heritable characteristics in both males and females. Method A 12-item scale, the SCDC, was completed by three independent samples drawn from a twin register, a group with Turner syndrome and children with a diagnosis of autistic-spectrum disorder attending clinics. The data were used to establish the heritability reliability and validity of the checklist. Results Traits measured by the SCDC were highly heritable in both genders (0.74). Internal consistency was excellent (0.93) and test-retest reliability high (0.81). Discriminant validity between pervasive developmental disorder and other clinical groups was good, discrimination from non-clinical samples was better; sensitivity (0.90), specificity (0.69). Conclusions The SCDC is a unique and efficient first-level screening questionnaire for autistic traits Declaration of interest None.

Smith, I. M., Nichols, S. L., Issekutz, K., & Blake, K. (2005). Behavioral profiles and symptoms of autism in CHARGE syndrome: Preliminary Canadian epidemiological data. *American Journal of Medical Genetics Part A*, *133A*(3), 248-256.

Individuals with CHARGE syndrome were identified through the Canadian Pediatric Surveillance Program (CPSP). From this population-based cohort (n = 78), we present data on developmental and behavioral characteristics for the first 13 individuals (eight males, five females) for whom assessments are complete. Standardized parent questionnaires on development and behavior were followed by a structured telephone interview, with a specific emphasis on symptoms of autistic spectrum disorder (ASD). Preliminary results confirm that individuals with CHARGE syndrome have relatively low adaptive behavior skills, motor impairments being particularly significant. Most individuals did not present with significant behavior problems; however, evidence of ASD symptoms was judged to be moderate to strong in six of the ten children who were above the age of 4-5 years. Results are discussed with reference to the challenges inherent in the diagnosis of autism in individuals with sensory impairments, and to the implications for understanding the etiology of CHARGE syndrome and of ASD.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive behavior profiles in Asperger syndrome and high-functioning autism. *Journal of Autism and Developmental Disorders*, *35*(2), 145-158.

Although repetitive behaviors are a core diagnostic domain for autism spectrum disorders, research in this area has been neglected. This study had two major aims (1) to provide a detailed characterization of repetitive behaviors in individuals with Asperger Syndrome (AS), high-functioning autism (HFA), and typically developing controls (TD); and (2) to examine whether differences in repetitive behavior profiles could provide evidence for the external validity of AS separate from HFA. Specifically, it was

hypothesized that circumscribed interests would be more prevalent and cause more impairment in the AS group than the HFA group, while the reverse would be true for other categories of repetitive behavior. The parent(s) of 61 children and adolescents (19 with AS, 21 with HFA, and 21 TD) completed two interviews focused specifically on lifetime and current repetitive behavior symptoms. No reliable differences in repetitive behavior between AS and HFA children were found. Results suggested that circumscribed interests differ in developmental course from the three other DSM-IV-TR categories of repetitive behavior. Internal consistency among the four DSM-IV-TR categories of repetitive behavior was high, $=.84$, providing evidence for a unitary repetitive behaviors factor. The importance of expanding research in the repetitive behavior domain is highlighted as part of the necessary integration of behavioral and neurobiological approaches to understanding the etiology of autism.

Starr, E. M., S. K. Berument, et al. (2005). "Brief report: Autism in individuals with Down syndrome." *Journal of Autism and Developmental Disorders* **35**(5): 665-673.

As an off-shoot of a study examining the reliability and validity of an adapted version of the Pre-Linguistic Autism Diagnostic Observation Schedule (A-PL-ADOS), 13 individuals with Down syndrome with IQs ranging between 24 and 48 were administered the Autism Diagnostic Interview-Revised (ADI-R) and the A-PL-ADOS, which are well-validated interview and observational diagnostic measures. Three out of 13 met lifetime criteria on the ADI-R, but none of these three showed behavior that met the criterion for autism on the APL-ADOS (although two nearly did so). However, two individuals did meet the A-PL-ADOS criterion and showed behavior that fell only just short of meeting lifetime criteria on the ADI-R. Altogether, 5 individuals with Down syndrome may be considered to show an autism spectrum disorder. Of the remaining 8, some showed a few autistic features, and some showed none. The findings raise both methodological and conceptual issues.

Stromland, K., Sjogreen, L., Johansson, M., Joelsson, B. M. E., Miller, M., Danielsson, S., et al. (2005). CHARGE association in Sweden: Malformations and functional deficits. *American Journal of Medical Genetics Part A*, *133A*(3), 331-339.

CHARGE association (CA) consists of a non-random association of ocular coloboma (C), heart anomaly (H), atresia of choanae (A), retarded growth and/or development (R), genital hypoplasia (G), and ear anomalies and/or hearing impairment (E). A prospective multidisciplinary study of 31 Swedish patients with CA was undertaken in order to describe the associated malformations and functional deficits, find possible etiological factors and identify critical time periods for the maldevelopment. The clinical files were analyzed, the mothers answered a questionnaire on history of prenatal events, and a clinical evaluation of systemic findings, vision, hearing, balance, speech, oral and swallowing function, and neuropsychiatric function, especially autism, was performed. The most frequent physical abnormalities affected ears (90%), eyes (90%), brain (61%), heart (52%), retarded growth (48%), genitals (38%), choanae (35%), and facial nerve (32%). Sixty-one percent of the patients were visually impaired or blind, and 74% had hearing loss or deafness. Problems in balance, speech, and eating were common. Forty percent of the patients had autism/atypical autism, and 82% had

developmental delay. Three children were born following assisted fertilization and two mothers had diabetes. The mothers reported infections, bleedings, and drug use during pregnancy. Analysis of possible critical time periods suggested that most malformations were produced early in pregnancy, mainly during post conceptual weeks 4, 5, and 6. A multidisciplinary approach is essential in the assessment and management of CA.

Tager-Flusberg, H. (2005). Designing studies to investigate the relationships between genes, environments, and developmental language disorders. *Applied Psycholinguistics*, 26(1), 29-39.

This paper focuses on designing studies that will compare children with developmental language disorders (DLD) drawn from several syndromes in which there are primary impairments in the acquisition of language. This kind of research can be used to address four key questions: (a) What are the developing language phenotypes that characterize specific disorders? (b) What factors are key precursors and predictors of language acquisition in DLD? (c) What are the genes that contribute to DLD in different syndromes? (d) What environmental factors influence the trajectories of language development in DLD? Several design issues are discussed including an overall study design, subject selection and recruitment, matching and comparisons across groups, and methodologies. A number of important challenges to the design and implementation of these kinds of studies are presented in the final section of the paper.

Towbin, K. E., A. Pradella, et al. (2005). "Autism spectrum traits in children with mood and anxiety disorders." *Journal of Child and Adolescent Psychopharmacology* 15(3): 452-464.

The autism spectrum disorders (ASDs) can present with symptoms commonly found in mood and anxiety disorders. The Social Communication Questionnaire (SCQ), Children's Communication Checklist (CCC-2), and the Social Reciprocity Scale (SRS) were used to screen children in a mood disorders research clinic setting for symptoms of ASD. Ninety-three patients (mean age, 12.7 +/- 2.8 years; percent male, 63%) completed at least one scale, and 50 children completed all three. The prevalence of those screening positive for a possible ASD on one instrument was 62% and on all three measures was 8%. Fifty-seven percent (n = 21/37; odds ratio, 4.59 [95% confidence interval (CI) = 1.40-15.111] of those scoring in the "ASD-likely" range on the SRS scored in that range on the CCC-2. Only 16% (n = 6/37; odds ratio, not significant (NS)) of those scoring in the ASD-likely range on the SRS, and 14% (n = 5/37; odds ratio, NS) of those scoring in the ASD-likely range on the CCC-2, scored similarly on the SCQ. These results demonstrate a need to develop valid and reliable instruments to screen for ASDs in children presenting outside of ASD clinics.

Veltman, M. W. M., E. E. Craig, et al. (2005). "Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review." *Psychiatric Genetics* 15(4): 243-254.

Autism spectrum disorders (ASDs) have been linked with maternally derived duplications/triplications of chromosome 15q11-13 and therefore might occur more frequently in people with Prader-Willi syndrome (PWS) when due to uniparental disomy (UPD), than in other forms of chromosomal abnormality involving this region [i.e.

deletion (DEL) forms of PWS and DEL+ UPD forms of Angelman's syndrome -(AS)]. Twelve studies regarding ASD in PWS and AS were reviewed. It was noteworthy that among the genetically confirmed UPD and DEL cases of PWS and AS, the rate of ASD was 25.3% (38/150; range 0-36.5%) in PWS and 1.9% in AS (2/104; range 0-100%) (Fisher's exact $P < 0.0001$). Among the subset of cases with confirmed UPD or DEL, the rate of ASD in the UPD cases of PWS was significantly higher (20/53) than in the remaining combined samples (i.e. DEL PWS+UPD AS+DEL AS cases; 20/201) (Fisher's exact $P < 0.0001$). ASD in UPD PWS cases (20/53) compared with DEL PWS cases (18/97) was also statistically significant (Fisher's exact $P=0.0176$). Thus, the limited available evidence supported the prediction that overexpression of maternally imprinted genes in 15q11-13 confers a risk for ASD. Further research will be required to confirm these findings. *Psychiatr Genet* 15:243-254 (c) 2005 Lippincott Williams & Wilkins.

Volkmar, F., Chawarska, K., & Klin, A. (2005). Autism in infancy and early childhood. *Annual Review of Psychology*, 56, 315-336.

Although initially described as an inborn disorder of affective contact, information on autism as it exists in infants has been limited. Delays in diagnosis, lack of information about the condition, and reliance on retrospective research strategies have been problematic. An awareness of the increased risk for siblings is now allowing the development of new, prospective approaches. Consistent with Kanner's original hypothesis, the available information strongly suggests a fundamental difficulty in the earliest social processes, which, in turn, impacts many other areas of development. New approaches to screening have lowered the age of initial diagnosis; this presents new challenges for early intervention. Directions for future research are highlighted.

Wakschlag, L. S., B. L. Leventhal, et al. (2005). "Defining the "Disruptive" in preschool behavior: What diagnostic observation can teach us." *Clinical Child and Family Psychology Review* 8(3): 183-201.

This paper presents the clinical/developmental framework underlying a new diagnostic observational tool, the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS). The special importance of observation for clinical assessment during the preschool period is delineated. The developmental rationale for a multi-dimensional assessment of disruptive behavior in young children, including problems in modulation of negative affect and low competence is discussed. The ways in which the DB-DOS will elucidate distinctions between normative and atypical behavior during this developmental period via (a) the integration of qualitative and quantitative dimensions of behavior within a clinically-sensitive coding system, (b) the observation of child behavior both within, and outside of, the parent-child context and (c) the use of specially designed tasks to "press" for clinically salient behaviors are addressed. The promise of this new method for yielding a more precise, developmentally based description of the phenotype of early onset disruptive behavior problems and for providing a standardized clinical tool for observational assessment of disruptive behavior in young children is presented. Large-scale validation of the measure is currently underway.

Werner, E. and G. Dawson (2005). "Validation of the phenomenon of autistic regression using home videotapes." Archives of General Psychiatry **62**(8): 889-895.

Context: To date, there has been no objective validation of the phenomenon of autistic regression early in life. Objective: To validate parental report of autistic regression using behavioral data coded from home videotapes of children with autism spectrum disorder (ASD) vs typical development taken at 12 and 24 months of age. Design: Home videotapes of 56 children's first and second birthday parties were collected from parents of young children with ASD with and without a reported history of regression and typically developing children. Child behaviors were coded by raters blind to child diagnosis and regression history. A parent interview that elicited information about parents' recall of early symptoms from birth was also administered. Setting: Participants were recruited from a multidisciplinary study of autism conducted at a major university. Participants: Fifteen children with ASD with a history of regression, 21 children with ASD with early-onset autism, and 20 typically developing children and their parents participated. Main Outcome Measures: Observations of children's communicative, social, affective, repetitive behaviors, and toy play coded from videotapes of the toddlers' first and second birthday parties. Results: Analyses revealed that infants with ASD with regression show similar use of joint attention and more frequent use of words and babble compared with typical infants at 12 months of age. In contrast, infants with, ASD with early onset of symptoms and no regression displayed fewer joint attention and communicative behaviors at 12 months of age. By 24 months of age, both groups of toddlers with ASD displayed fewer instances of word use, vocalizations, declarative pointing, social gaze, and orienting to name as compared with typically developing 24-month-olds. Parent interview data suggested that some children with regression displayed difficulties in regulatory behavior before the regression occurred. Conclusion: This study validates the existence of early autistic regression.

Werner, E., G. Dawson, et al. (2005). "Variation in early developmental course in autism and its relation with behavioral outcome at 3-4 years of age." Journal of Autism and Developmental Disorders **35**(3): 337-350

The aims of the present study were to describe variations in the early course of development in autism by utilizing an in-depth parent interview that incorporated techniques to improve accuracy of parent recall, and to examine the relation between variations in early developmental course in autism and behavioral outcome at 3-4 years of age. The Early Development Interview, which consisted of questions about child's behavior in several domains from birth through 2 years of age, was created and administered to parents of 72 3-4-year-old children with autism spectrum disorder and 34 3-4-year-old children with developmental delay, who were matched on mental and chronological age, and 39 1-4-year-old typically developing children, who were matched to the clinical groups on mental age. At 3-4 years of age, children were administered standardized measures (some clinician administered and some parent report); these included verbal and nonverbal IQ, autism symptom severity, and adaptive and aberrant behavior. Based on the Early Development Interview, children with autism spectrum disorder (ASD) were reported to have elevated symptoms in the social and regulatory

domains by 3-6 months. By 12-15 months, parents of children with ASD reported significantly higher levels of social symptoms than parents of children with developmental delay. At 3-4 years of age, children with autism with early vs. late onset of symptoms, and with vs. without a history of loss of skills (regression) were not found to differ on standardized tests of verbal and nonverbal IQ and observational measures of autism symptom severity.

Williams, D. L., Goldstein, G., Carpenter, P. A., & Minshew, N. J. (2005). Verbal spatial working memory in autism. *Journal of Autism and Developmental Disorders*, 35(6), 747-756.

Verbal and spatial working memory were examined in high-functioning children, adolescents, and adults with autism compared to age and cognitive-matched controls. No deficit was found in verbal working memory in the individuals with autism using an N-back letter task and standardized measures. The distinction between the N-back task and others used previously to infer a working memory deficit in autism is that this task does not involve a complex cognitive demand. Deficits were found in spatial working memory. Understanding the basis for the dissociation between intact verbal working memory and impaired spatial working memory and the breakdown that occurs in verbal working memory as information processing demands are increased will likely provide valuable insights into the neural basis of autism.

Williams, D. L., Goldstein, G., & Minshew, N. J. (2005). Impaired memory for faces and social scenes in autism: clinical implications of memory dysfunction. *Archives of Clinical Neuropsychology*, 20(1), 1-15.

A clinical memory test, the Wechsler Memory Scale-III (WMS-III), was used to study the auditory and visual memory of 29 high-functioning adults with autism and 34 group-matched normal controls. The individuals with autism performed as well as the controls on immediate and delayed memory for word pairs and stories and on a verbal working memory task. The autism group was impaired on immediate and delayed recall of faces and of family scenes and had impaired spatial working memory. The integrity of verbal working memory and impaired spatial working memory is consistent with the findings of other studies and may reflect the greater computational demands of the spatial task. Most importantly, the deficits in memory for faces and common social scenes, complex visual/spatial stimuli, demonstrate the contribution of memory dysfunction in autism to deficits in real life function.

Williams, J., Scott, F., Stott, C., Allison, C., Bolton, P., Baron-Cohen, S., et al. (2005). The CAST (Childhood Asperger and Syndrome Test) - Test accuracy. *Autism*, 9(1), 45-68.

The Childhood Asperger Syndrome Test (CAST) is a KEYWORDS parental questionnaire to screen for autism spectrum conditions. In autistic this validation study, the CAST was distributed to 1925 children aged disorders; 5-11 in mainstream Cambridgeshire schools. A sample of participants childhood received a full diagnostic assessment, conducted blind to screen status. e sensitivity of the CAST, at a designated cut-point of 15 was 100, percent, the specificity was 97 percent and the positive

predictive value disorders; was 50 percent, using the group's consensus diagnosis as the gold pervasive standard. The accuracy indices varied with the case definition used. The disorders; sensitivity of the accuracy statistics to case definition and to missing screening data was explored. The CAST is useful as a screening test for autism spectrum conditions in epidemiological research. There is not currently enough evidence to recommend the use of the CAST as a screening test within a public ! health screening programme in the general population.

Woodbury-Smith, M. R., J. Robinson, et al. (2005). "Screening adults for asperger syndrome using the AQ: A preliminary study of its diagnostic validity in clinical practice." *Journal of Autism and Developmental Disorders* **35**(3): 331-335

The Autism Spectrum Quotient (AQ) has been developed to measure the degree to which an adult with normal intelligence has autistic traits. In this paper it is evaluated for its potential as a screening questionnaire in clinical practice on one hundred consecutive referrals to a diagnostic clinic for adults suspected of having Asperger Syndrome or high functioning autism (AS/HFA). The results indicate that it has good discriminative validity and good screening properties at a threshold score of 26. The implications of these results are discussed.

Wright, B., Brzozowski, A. M., Calvert, E., Farnworth, H., Goodall, D. M., Holbrook, I., et al. (2005). Is the presence of urinary indolyl-3-acryloylglycine associated with autism spectrum disorder? *Developmental Medicine and Child Neurology*, *47*(3), 190-192..

To test whether the presence of indolyl-3-acryloylglycine (IAG) is associated with autism, we analyzed urine from population-based, blinded cohorts. All children in York, UK with autism spectrum disorders (ASDs), diagnosed using ICD-10 research diagnostic criteria, were invited to participate. Fifty-six children on the autism spectrum (mean age 9y 8mo, SD 3y 8mo; 79% male) agreed to participate, as did 155 children without ASDs (mean age 10y, SD 3y 2mo; 54% male) in mainstream and special schools (56 of whom were age-, sex-, and school-matched to children with ASDs). IAG was found at similar levels in the urine of all children, whether IAG concentrations or IAG:creatinine ratios were compared. There was no significant difference between the ASD and the comparison group, and no difference between children at mainstream schools and those at special schools. There is no association between presence of IAG in urine and autism; therefore, it is unlikely to be of help either diagnostically or as a basis for recommending therapeutic intervention with dietary manipulation. The significance of the presence of IAG in urine has yet to be determined.

Young, E. C., Diehl, J. J., Morris, D., Hyman, S. L., & Bennetto, L. (2005). The use of two language tests to identify pragmatic language problems in children with autism spectrum disorders. *Language Speech and Hearing Services in Schools*, *36*(1), 62-72.

Purpose: Pragmatic language disorders (PLDs) are difficult to diagnose in a cost-effective manner, and there are few assessment tools that yield quantitative data. This investigation was designed to determine whether two formal assessment tools would differentiate PLDs in children with autism spectrum disorders (ASDs) from controls matched on verbal IQ and language fundamentals. Method: Thirty-four matched participants were given the Test of Pragmatic Language (TOPL; D. Phelps-Terasaki & T. Phelps-Gunn, 1992) and the Strong Narrative Assessment Procedure (SNAP; C. J. Strong, 1998). Results: Participants with ASDs had significantly poorer scores than controls on the TOPL. On the SNAP, the children with ASDs performed similarly to controls on syntax, cohesion, story grammar, and completeness of episodes. The controls performed significantly better only on the ability to answer inferential questions. Clinical Implications: The TOPL was effective in differentiating PLDs in children with ASDs when performance was compared to matched controls. The SNAP did not clearly differentiate language problems in these two groups. Research is needed to develop formal assessment tools that target the unique language disabilities of high-functioning individuals with ASDs.

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience*, 23(2-3), 143-152.

In the interest of more systematically documenting the early signs of autism, and of testing specific hypotheses regarding their underlying neurodevelopmental substrates, we have initiated a longitudinal study of high-risk infants, all of whom have an older sibling diagnosed with an autistic spectrum disorder. Our sample currently includes 150 infant siblings, including 65 who have been followed to age 24 months, who are the focus of this paper. We have also followed a comparison group of low-risk infants. Our measures include a novel observational scale (the first, to our knowledge, that is designed to assess autism-specific behavior in infants), a computerized visual orienting task, and standardized measures of temperament, cognitive and language development. Our preliminary results indicate that by 12 months of age, siblings who are later diagnosed with autism may be distinguished from other siblings and low-risk controls on the basis of: (1) several specific behavioral markers, including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors; (2) prolonged latency to disengage visual attention; (3) a characteristic pattern of early temperament, with marked passivity and decreased activity level at 6 months, followed by extreme distress reactions, a tendency to fixate on particular objects in the environment, and decreased expression of positive affect by 12 months; and (4) delayed expressive and receptive language. We discuss these findings in the context of various neural networks thought to underlie neurodevelopmental abnormalities in autism, including poor visual orienting. Over time, as we are able to prospectively study larger numbers and to examine interrelationships among both early-developing behaviors and biological indices of interest, we hope this work will advance current understanding of the neurodevelopmental origins of autism.

Published 2004

Akshoomoff, N., C. Lord, et al. (2004). "Outcome classification of preschool children with autism spectrum disorders using MRI brain measures." *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(3), 349-357.

Objective: To test the hypothesis that a combination of magnetic resonance imaging (MRI) brain measures obtained during early childhood distinguish children with autism spectrum disorders (ASD) from typically developing children and is associated with functional outcome. **Method:** Quantitative MRI technology was used to measure gray and white matter volumes (cerebrum and cerebellum), total brain volume, and the area of the cerebellar vermis in 52 boys with a provisional diagnosis of autism (aged 1.9-5.2 years) and 15 typically developing young children (aged 1.7-5.2 years). Diagnostic confirmation and cognitive outcome data were obtained after the children reached 5 years of age. **Results:** A discriminant function analysis of the MRI brain measures correctly classified 95.8% of the ASD cases and 92.3% of the control cases. This set of variables also correctly classified 85% of the ASD cases as lower functioning and 68% of the ASD cases as higher functioning. **Conclusions:** These results indicate that variability in cerebellar and cerebral size is correlated with diagnostic and functional outcome in very young children with ASD.

Bolton, P.F., Veltman M.W., et al. (2004). Chromosome 15q11-13 abnormalities and other medical conditions in individuals with autism spectrum disorders. *Psychiatric Genetics*, 14(3), 131-137.

OBJECTIVES: The frequency of abnormalities of 15q11-q13 and other possibly causal medical disorders including karyotypic abnormalities was investigated in an unselected series of children who were referred to one of two autism assessment centres. **METHODS:** Two hundred and twenty-one cases were assessed using the Autism Diagnostic Interview and Observation Schedule and, where appropriate, standardized tests of intelligence and language abilities. Medical histories and notes were reviewed, and molecular and cytogenetic investigations used to detect chromosomal abnormalities. **RESULTS:** One hundred and eighty-one cases were diagnosed according to International Classification of Diseases - version 10 criteria as having an autism spectrum disorder (autistic-like Pervasive Developmental Disorder) and 40 cases as having other disorders. Twenty-one (11.6%) of the children with autism spectrum disorders had a possibly causal condition compared with six (15%) of the children with other diagnoses. One child with an autism spectrum disorder had a paternally inherited familial duplication of 15q11-13. The pattern of genotype-phenotype correlation within the family indicated that this form of abnormality might carry a risk for developmental difficulties, although the risk did not appear to be specific for autism spectrum disorders. **CONCLUSION:** The overall rate of possibly causal medical and cytogenetic conditions in children with autism spectrum disorders was low and no different from the rate of disorder in children with other

developmental/neuropsychiatric disorders that attended the same clinics. Further research is required to determine whether paternal duplication of 15q11-13 gives rise to adverse developmental outcomes.

Bradley, E. A., J. A. Summers, et al. (2004). "Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism." *Journal of Autism and Developmental Disorders*, 34(2), 151-161.

Eight males and four females with an Autism Diagnostic Interview-Revised (ADI-R) diagnosis of autism (mean age of 16.3 years) and severe intellectual disability (IQ < 40) were individually matched to controls on the basis of chronological age, gender, and nonverbal IQ. The dependent measure was the Diagnostic Assessment for the Severely Handicapped-II, which is used to screen for psychiatric and behavior disorders in lower-functioning individuals. Participants with autism showed significantly greater disturbances as measured by the Diagnostic Assessment for the Severely Handicapped-II total score and seven of 13 subscales. They also averaged 5.25 clinically significant disturbances compared with 1.25 disturbances for participants without autism. Specific vulnerabilities to anxiety, mood, sleep, organic syndromes, and stereotypies/tics were found in the participants with comorbid autism.

Buxbaum, J. D., J. Silverman, et al. (2004). "Linkage analysis for autism in a subset families with obsessive-compulsive behaviors: Evidence for an autism susceptibility gene on chromosome 1 and further support for susceptibility genes on chromosome 6 and 19." *Molecular Psychiatry*, 9(2), 144-150.

Although there is considerable evidence for a strong genetic component to idiopathic autism, several genome-wide screens for susceptibility genes have been carried out with limited concordance of linked loci, reflecting numerous genes of weak effect and/or sample heterogeneity. In the current study, linkage analysis was carried out in a sample of 62 autism-affected relative pairs with more severe obsessive - compulsive behaviors, selected from a larger (n = 115) set of autism-affected relative pairs as a means of reducing sample heterogeneity. Obsessive - compulsive behaviors were assessed using the Autism Diagnostic Interview-Revised (ADI-R). In the sample with more severe obsessive - compulsive behaviors, multipoint NPL scores above 2 were observed on chromosomes 1, 4, 5, 6, 10, 11 and 19, with the strongest evidence for linkage on chromosome 1 at the marker D1S1656, where the multipoint NPL score was 3.06, and the two-point NPL score was 3.21. In follow-up analyses, analyzing the subset of families (n = 35) where the patients had the most severe obsessive compulsive behaviors generated a multipoint NPL score of 2.76, and a two-point NPL score of 2.79, indicating that the bulk of evidence for linkage was derived from the families most severely affected with obsessive - compulsive behaviors. The data suggest that there is an autism susceptibility gene on chromosome 1 and provide further support for the presence of autism susceptibility genes on chromosomes 6 and 19.

Coutinho, A. M., Oliveira, G., Morgadinho, T., Fesel, C., Macedo, T. R., Bento, C., et al. (2004). Variants of the serotonin transporter gene (SLC6A4) significantly contribute to hyperserotonemia in autism. *Molecular Psychiatry*, 9(3), 264-271.

The role of the serotonin system in the etiology and pathogenesis of autism spectrum disorders (ASD) is not clearly defined. High levels of platelet serotonin (5-HT) have been consistently found in a proportion of patients, and it is known that specific 5-HT transporter gene (SLC6A4) variants modulate transporter reuptake function, therefore possibly influencing the occurrence of hyperserotonemia in a subset of autistic patients. We have examined the association of platelet serotonin levels with two SLC6A4 polymorphisms, 5-HTT gene-linked polymorphic region (HTTLPR) in the promoter and intron 2 variable number of tandem repeats (VNTR), in a sample of 105 ASD patients, their parents, and 52 control children. Quantitative transmission disequilibrium test (QTDT) results showed a significant effect on 5-HT levels of each SLC6A4 marker ($P=0.017$ for HTTLPR; $P=0.047$ for intron 2 VNTR) and of haplotypes of the two markers ($P=0.017$), with a major contribution of the L. Stin2.10 haplo! type ($P=0.0013$). A 5-HT mean value in the range of hyperserotonemia was associated with the homozygous L. Stin2.10 haplotype ($H(1,N=97)=7.76$, $P=0.0054$), which occurred in 33% of hyperserotonemic patients against 6% of patients with normal 5-HT levels (Fisher's exact test: $P=0.013$, $OR=8$). Allele interaction at the HTTLPR locus was found, with a significant dominance variance effect on 5-HT levels. We found no transmission disequilibrium of any of the SLC6A4 variants in ASD. Our results show that the SLC6A4 gene is a significant factor in the determination of 5-HT levels, and that specific SLC6A4 variants are associated with an increased risk for hyperserotonemia in our sample of autistic patients. The biological mechanism, however, is unlikely to involve the SLC6A4 gene solely. The associated SLC6A4 alleles likely interact with other genes or environmental factors to produce the abnormally high 5-HT levels observed in this subset of autistic patients, who possibly represent a separate etiological group.

Devlin, B., Bennett, P., Dawson, G., Figlewicz, D. A., Grigorenko, E. L., McMahon, W., et al. (2004). Alleles of a Reelin CGG repeat do not convey liability to autism in a sample from the CPEA network. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, 126B(1), 46-50.

A recent study by Persico et al. [2001: *Mol Psychiatry* 6:150-159] suggests alleles of a CGG polymorphism, just 5' of the reelin gene (RELN) initiator codon, confer liability for autism, especially alleles bearing 11 or more CGG repeats (long alleles). The association is consistent across both a case-control and family-based sample. We attempted to replicate their finding using a larger, independent family-based sample from the NIH Collaborative Programs of Excellence in Autism (CPEA) Network. In our data, allele transmissions to individuals with autism versus unaffected individuals are unbiased, both when alleles are classified by repeat length and when they are classified into long/short categories. Because of the apparent linkage of autism to chromosome 7q, particularly related to the development of language, we also evaluate the relationship between Reelin alleles and the age at which autism subjects use their first word or first phrase. Neither is significantly associated with Reelin alleles. Our results are not consistent with a major role for Reelin alleles in liability to autism.

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., et al. (2004). Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Developmental Psychology*, 40(2), 271-283.

This study investigated social attention impairments in *autism* (social orienting, joint attention, and attention to another's distress) and their relations to language ability. Three- to four-year-old children with *autism* spectrum disorder (ASD; n = 72), 3- to 4-year-old developmentally delayed children (n = 34), and 12- to 46-month-old typically developing children (n = 39), matched on mental age, were compared on measures of social orienting, joint attention, and attention to another's distress. Children with *autism* performed significantly worse than the comparison groups in all of these domains. Combined impairments in joint attention and social orienting were found to best distinguish young children with ASD from those without ASD. Structural equation modeling indicated that joint attention was the best predictor of concurrent language ability. Social orienting and attention to distress were indirectly related to language through their relations with joint attention. These results help to clarify the nature of social attention impairments in autism, offer clues to developmental mechanisms, and suggest targets for early intervention.

Hrdlicka, M., V. Komarek, et al. (2004). Not EEG abnormalities but epilepsy is associated with autistic regression and mental functioning in childhood autism. *European Child & Adolescent Psychiatry* 13(4): 209-213.

The aim of the study was to investigate the potential association of epilepsy and EEG abnormalities with autistic regression and mental retardation. We examined a group of 77 autistic children (61 boys, 16 girls) with an average age of 9.1 +/- 5.3 years. Clinical interview, neurological examination focused on the evaluation of epilepsy, IQ testing, and 21-channel EEG (including night sleep EEG recording) were performed. Normal EEGs were observed in 44.4% of the patients, non-epileptiform abnormal EEGs in 17.5%, and abnormal EEGs with epileptiform discharges in 38.1% of the patients. Epilepsy was found in 22.1% of the subjects. A history of regression was reported in 25.8% of the patients, 54.8% of the sample had abnormal development during the first year of life, and 79.7% of the patients were mentally retarded. Autistic regression was significantly more frequent in patients with epilepsy than in non-epileptic patients (p = 0.003). Abnormal development during the first year of life was significantly associated with epileptiform EEG abnormalities (p = 0.014). Epilepsy correlated significantly with mental retardation (p = 0.001). Although the biological basis and possible causal relationships of these associations remain to be explained, they may point to different subgroups of patients with autistic spectrum disorders.

Humphrey, A., Higgins, J. N. P., Yates, J. R. W., & Bolton, P. F. (2004). Monozygotic twins with tuberous sclerosis discordant for the severity of developmental deficits. *Neurology*, 62(5), 795-798.

A pair of monozygotic male twins with tuberous sclerosis (TS) were followed between 18 months and 3 years of age. Twin A with 25 large cortical tubers and hence extensive brain involvement was moderately mentally retarded and met criteria for autism. The other twin had more (n = 31) but smaller tubers. He was not mentally retarded and did not meet criteria for autism. This study provides evidence that

nongenetic factors such as extent of brain abnormality and not just number of cortical tubers are important in determining phenotypic variability in TS. The findings also raise questions about the mechanisms giving rise to autism in TS.

Joseph, R. M. and H. Tager-Flusberg (2004). "The relationship of theory of mind and executive functions to symptom type and severity in children with autism." *Development and Psychopathology*, 16(1), 137-155.

Although neurocognitive impairments in theory of mind and in executive functions have both been hypothesized to play a causal role in autism, there has been little research investigating the explanatory power of these impairments with regard to autistic symptomatology. The present study examined the degree to which individual differences in theory of mind and executive functions could explain variations in the severity of autism symptoms. Participants included 31 verbal, school-aged children with autism who were administered a battery of tests assessing the understanding of mental states (knowledge and false belief) and executive control skills (working memory, combined working memory and inhibitory control, and planning) and who were behaviorally evaluated for autism severity in the three core symptom domains. Whereas theory of mind and executive control abilities explained the significant variance beyond that accounted for by language level in communication symptoms, neither explained the significant variance in reciprocal social interaction or repetitive behaviors symptoms. These findings are discussed in terms of a proposed distinction between higher level, cognitive-linguistic aspects of theory of mind and related executive control skills, and more fundamental social-perceptual processes involved in the apprehension of mental state information conveyed through eyes, faces, and voices, which may be more closely linked to autistic deficits in social reciprocity.

Kates, W. R., C. P. Burnette, et al. (2004). "Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism." *American Journal of Psychiatry*, 161(3), 539-546.

Objective: The broader autism phenotype includes relatives of individuals with autism who display social and language deficits that are qualitatively similar to those of autism but less severe. In previous studies of monozygotic twins discordant for autism, more than 75% of the twins without autism displayed the broader phenotype. Differences in neuroanatomy between discordant monozygotic twins might be associated with the narrow and broader behavioral phenotypes. The authors examined the relationship of twin pair differences in clinical phenotype to differences in neuroanatomic phenotype. **Method:** The subjects were 16 monozygotic twin pairs between the ages of 5 and 14 years and 16 matched singleton comparison subjects. Seven twin pairs were clinically concordant and nine twin pairs were clinically discordant for strictly defined autism. After magnetic resonance imaging, a semiautomated procedure was applied to images in which the brain tissue was subdivided into neurofunctional regions and segmented into gray, white, and ventricular compartments. **Results:** Both the concordant and discordant twin pairs exhibited concordance in cerebral gray and white matter volumes. However, only the clinically concordant pairs exhibited concordance in cerebellar gray and white matter volumes. within the discordant twin pairs, both the twins with autism and their co-

twins exhibited frontal, temporal, and occipital white matter volumes that were lower than those of the comparison subjects. Conclusions: These findings support the role and the limits of genetic liability in autism. Continuing to clarify the neuroanatomic pathways in autistic spectrum disorders could illuminate the etiology of autism and, ultimately, contribute to treatments.

Kau, A. S. M., Tierney, E., Bukelis, I., Stump, M. H., Kates, W. R., Trescher, W. H., et al. (2004). Social behavior profile in young males with fragile X syndrome: Characteristics and specificity. *American Journal of Medical Genetics Part A*, 126A(1), 9-17.

The present study characterizes distinctive and specific features of social behavior impairment, termed social behavior profile (SBP), in young males with fragile X syndrome (FraX). Fourteen males with FraX and autism (FraX+Aut), ages 3-8 years, were compared with either 41 FraX boys without autism (Aut), 7 age-matched males with developmental language delay and autism (DLD+Aut), or with 11 boys with non-selected (for language delay) idiopathic autism (IA), on several standardized instruments assessing social behavior and autistic features (i.e., autism diagnostic interview-revised, ADI-R). We found that FraX+Aut subjects displayed more impairment in overall cognition, problem/aberrant behavior, and adaptive behavior than the rest of the FraX cohort, even when individuals with pervasive developmental disorder (PDD) were included in the latter. Compared to both DLD+Aut and IA, FraX+Aut males were less impaired in ADI-R reciprocal social interaction (RECS) domain. However, boys with FraX+Aut were in general comparable to DLD+Aut subjects in problem/aberrant and adaptive behaviors. Based on the contrast between FraX+Aut and non-autistic FraX and DLD+Aut, we were able to identify measures (e.g., child behavior checklist (CBCL) withdrawn subscale) that better define social interaction impairment in FraX. Comparisons with DLD+Aut and IA led to the conclusion that communication impairment (COMM) and stereotypic behavior contribute relatively more to the diagnosis of autism in FraX+Aut. In agreement with recent studies, our data suggest that FraX+Aut, and more generally SBP, is a distinctive subphenotype among boys with FraX, which may share some pathophysiological mechanisms with IA.

Kaufmann, W. E., Cortell, R., Kau, C. S. M., Bukelis, I., Tierney, E., Gray, R. M., et al. (2004). Autism spectrum disorder in fragile X syndrome: Communication, social interaction, and specific behaviors. *American Journal of Medical Genetics Part A*, 129A(3), 225-234.

The present study extends our previous work on social behavior impairment in young males with fragile X syndrome (FraX). Specifically, we evaluated whether the autistic phenomenon in FraX is expressed as a range of behavioral impairments as in idiopathic autism (Aut). We also examined whether there are behaviors, identified as items of the Autism Diagnostic Interview-Revised (ADI-R), that in FraX predispose to or differentiate subjects with autism spectrum disorder (ASD) diagnosis. Finally, regression models were utilized to test the relative contribution of reduced communication and socialization skills to ADI-R scores and diagnoses. A cohort of 56 boys (3-8 years) with FraX was examined in terms of scores on measures of cognition (IQ was a co-variate in

most analyses.), autistic behavior, problem/aberrant behavior, adaptive behavior, and language development. We found that, indeed, in terms of problem behavior and adaptive skills, there is a range of severity from FraX + Aut to FraX + PDD (Pervasive Developmental Disorder) to FraX + none. ADI-R items representing "Play" types of interaction appear to be "susceptibility" factors since they were abnormal across the FraX cohort. Integrated regression models demonstrated that items reflecting complex social interaction differentiated the FraX + ASD (Aut + PDD) subgroup from the rest of the FraX cohort, while abnormalities in basic verbal and non-verbal communication distinguished the most severely affected boys with FraX + Aut from the milder FraX + PDD cohort. Models incorporating language, adaptive communication, and adaptive socialization skills revealed that socialization was not only the main influence on scores but also a predictor of ASD diagnosis. Altogether, our findings demonstrate that the diagnosis of ASD in FraX reflects, to a large extent, an impairment in social interaction that is expressed with variable severity in young males with FraX.

Li, J., Nguyen, L., Gleason, C., Lotspeich, L., Spiker, D., Risch, N., et al. (2004). Lack of evidence for an association between WNT2 and RELN polymorphisms and autism. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, 126B(1), 51-57.

Autism is a pervasive neurodevelopmental disorder characterized by deficits in language development and social interaction, as well as stereotypical, repetitive behaviors. The etiology of autism is largely unknown. Family and twin studies have provided compelling evidence for a strong genetic component in most idiopathic cases. Several recent candidate gene studies have suggested that alleles of WNT2 and the reelin gene (RELN), two genes involved in distinct aspects of neurodevelopment, confer greater susceptibility to autism. We screened WNT2 for DNA polymorphisms by sequencing all exons and adjacent intronic regions in 24 autistic patients, and identified not only the WNT2 variants reported previously (two common single-nucleotide polymorphisms (SNPs) in the 5' upstream region and the 3' untranslated region (UTR), respectively), but also two new SNPs in its 3' UTR. We genotyped all four WNT2 polymorphisms and a polymorphic trinucleotide repeat in the 5' UTR of RELN in 107 families with multiple autistic children, and evaluated evidence for association between these variants and autism by the transmission disequilibrium test (TDT). Our results revealed no deviation from the null hypothesis of no association. Our interpretation of these findings is that it is unlikely that DNA variations in RELN and WNT2 play a significant role in the genetic predisposition to autism.

Laumonier, F., Bonnet-Brilhault, F., Gomot, M., Blanc, R., David, A., Moizard, M. P., et al. (2004). X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *American Journal of Human Genetics*, 74(3), 552-557.

A large French family including members affected by nonspecific X-linked mental retardation, with or without autism or pervasive developmental disorder in affected male patients, has been found to have a 2-base-pair deletion in the Neuroligin 4

gene (NLGN4) located at Xp22.33. This mutation leads to a premature stop codon in the middle of the sequence of the normal protein and is thought to suppress the transmembrane domain and sequences important for the dimerization of neuroligins that are required for proper cell-cell interaction through binding to beta-neurexins. As the neuroligins are mostly enriched at excitatory synapses, these results suggest that a defect in synaptogenesis may lead to deficits in cognitive development and communication processes. The fact that the deletion was present in both autistic and nonautistic mentally retarded males suggests that the NLGN4 gene is not only involved in autism, as previously described, but also in mental retardation, indicating that some types of autistic disorder and mental retardation may have common genetic origins.

Lord, C., Shulman, C., & DiLavore, P. (2004). Regression and word loss in autistic spectrum disorders. *Journal of Child Psychology and Psychiatry*, 45(5), 936-955.

Background: For many years, researchers and clinicians have described parent reports of an unusual developmental phenomenon in a substantial minority of children with Autistic Spectrum Disorders (ASD), the acquisition and then loss of communication skills during the second year of life. Methods: As part of a longitudinal study of 110 children referred for assessments of possible autism at age 2 years or younger, 21 developmentally delayed children and 33 typically developing controls, 19 children were described by their parents at age 2 as having gained and lost spontaneous, meaningful words, and 12 children as having a history of less specific loss of imitated words or nonword vocalizations. A battery of diagnostic and cognitive tasks was administered to all children at study entrance, at ages 3 (for the referral children only) and 4 or 5 (for referral and developmentally delayed children). Results: Results indicated that the acquisition of a small number of spontaneous words used meaningfully and consistently followed by loss of all words, often associated with other social changes, was unique to children diagnosed at 5 years with ASD. Few differences, besides those that defined the pattern of word loss, emerged between children with ASD with and without word loss. Loss of less specific, nonword vocalizations was associated with cognitive delay, with or without autism. Conclusions: Word loss is a reliably identifiable phenomenon in early childhood that appears to be unique, but not universal to, ASD. Histories and outcome of children with word loss were not in keeping with a sudden change from normal to abnormal functioning, but did suggest that this type of loss in the second year of life may be a useful 'red flag' for ASD in a significant minority of cases.

Lord, C., Risi, S., Pickles, A. (2004). Trajectory of Language Development in Autistic Spectrum Disorders. In: Rice, M. L., Steven, S. F., *Developmental language disorders: From phenotypes to etiologies*. Mahwah, New Jersey: Lawrence Erlbaum Associates, Publishers, 7-29.

(from the chapter) Notes that there are many aspects of language delay that have significant implications for our understanding of autistic spectrum disorders. To date most research on the relation between language and autism has used general measures of verbal functioning. However, studies that have incorporated numerous measures have shown high correlations between receptive and expressive language measures as well as with early developmental measures. Methodologically, it is a challenge to measure

change in skills using standardized measures that necessarily shift as the skills reconfigure, and this has limited our knowledge about trajectories of language development over time. However, there are currently a number of creative attempts to develop methods that minimize these difficulties. It is also important to distinguish between the effect of the level of language impairment and the effects of absolute language level--either expressive or receptive, or both--on other behaviors because this affects how we view the relation between language and behaviors associated with autism. Recently, many of the studies on language and autism primarily control the effect of language development to address the broader conceptualizations of cognition and social development such as theory of mind or central coherence. This strategy has been important in improving our understanding of the specificity of various cognitive deficits in autism. However, it now seems time to step back and take a more serious look at the unique trajectories of language development that may occur in autistic spectrum disorders. These trajectories may have important implications for understanding the etiology, nature of change, and potential response to treatment in autistic spectrum disorders.

Lotspeich, L., Kwon, H., Schumann, C. M., Fryer, S. L., Goodlin-Jones, B. L., Buonocore, M. H., et al. (2004). Investigation of neuroanatomical differences between autism and Asperger syndrome. *Archives of General Psychiatry*, 61(3), 291-298.

Background: Autism and Asperger syndrome (ASP) are neurobiological conditions with overlapping behavioral symptoms and of unknown etiologies. Results from previous autism neuroimaging studies have been difficult to replicate, possibly owing to site differences in subject samples, scanning procedures, and image-processing methods. We sought (1) to determine whether low-functioning autism (LFA; IQ < 70), high-functioning autism (HFA; IQ greater than or equal to 70), and ASP constitute distinct biological entities as evidenced by neuroanatomical measures, and (2) to assess for intersite differences. Methods: Case-control study examining coronally oriented 124-section spoiled gradient echo images acquired on 3 magnetic resonance imaging (MRI) systems, and processed by BrainImage 5X. Participants were recruited and underwent scanning at 2 academic medicine departments. Participants included 4 age-matched groups of volunteer boys aged 7.8 to 17.9 years (13 patients with LFA, 18 with HFA, 21 with ASP, and 21 control subjects), and 3 volunteer adults for neuroimaging reliability. Main outcome measures included volumetric measures of total, white, and gray matter for cerebral and cerebellar tissues. Results: Intersite differences were seen for subject age, IQ, and cerebellum measures. Cerebral gray matter volume was enlarged in both HFA and LFA compared with controls ($P=.009$ and $P=.04$, respectively). Cerebral gray matter volume in ASP was intermediate between that of HFA and controls, but nonsignificant. Exploratory analyses revealed a negative correlation between cerebral gray matter volume and performance IQ within HFA but not ASP. A positive correlation between cerebral white matter volume and performance IQ was observed within ASP but not HFA. Conclusions: Lack of replication between previous autism MRI studies could be due to intersite differences in MRI systems and subjects' age and IQ. Cerebral gray matter findings suggest that ASP is on the mild end of the autism spectrum. However, exploratory assessments of brain-IQ relationships reveal differences between HFA and ASP, indicating that these conditions may be neurodevelopmentally different when

patterns of multiple measures are examined. Further investigations of brain-behavior relationships are indicated to confirm these findings.

McPartland J., G. Dawson, et al. (2004). Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. *Journal of Child Psychology and Psychiatry* 45(7): 1235-1245.

BACKGROUND: Individuals with autism exhibit impairments in face recognition, and neuroimaging studies have shown that individuals with autism exhibit abnormal patterns of brain activity during face processing. The current study examined the temporal characteristics of face processing in autism and their relation to behavior. **METHOD:** High-density event-related brain potentials (ERPs) were recorded to images of faces, inverted faces, and objects from 9 individuals with autism spectrum disorder (15-42 years old) and 14 typical individuals (16-37 years old). **RESULTS:** With respect to a face-sensitive ERP component (N170), individuals with autism exhibited longer N170 latencies to faces than typical individuals but comparable latencies to objects. Typical individuals exhibited longer N170 latencies to inverted as compared to upright faces, whereas individuals with autism did not show differences in N170 latency to upright versus inverted faces. Neural speed of face processing, as reflected in N170 latency, correlated with performance on a face recognition task for individuals with autism. **CONCLUSIONS:** These data provide evidence for slowed neural speed of face processing in autism and highlight the role of speed of processing in face processing impairments in autism.

Mulder, E. J., Anderson, G. M., Kema, I. P., de Bildt, A., van Lang, N. D. J., den Boer, J. A., et al. (2004). Platelet serotonin levels in pervasive developmental disorders and mental retardation: Diagnostic group differences, within-group distribution, and behavioral correlates. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(4), 491-499.

Objective: To investigate group differences, the within-group distributions, and the clinical correlates of platelet serotonin (5-HT) levels in pervasive developmental disorders (PDD). **Method:** Platelet 5-HT levels were measured in Dutch children and young adults, recruited from 2001 through 2003, with PDD (autism, Asperger's, and PDD-not otherwise specified [PDD-NOS]; n = 81) or with mental retardation (MR; n = 54) but without PDD, and in normal controls (n = 60). The distribution of platelet 5-HT levels was assessed using mixture-modeling analyses. Relationships between platelet 5-HT levels and a full range of demographic, clinical, and behavioral variables were examined. **Results:** Group mean (+/- SD) platelet 5-HT levels (nmol/10⁹ platelets) were significantly higher in the autistic (4.51 +/- 1.61, n = 33) and PDD-NOS (4.90 +/- 1.54, n = 43) groups compared to the MR (3.48 +/- 1.33, n = 54) or the normal control (3.58 +/- 1.08, n = 60) groups (F-4,F-190 = 9.35, p < .001).! Platelet 5-HT values in the combined PDD group showed a bimodal distribution, and an empirical cutpoint for hyperserotonemia was determined. None of the behavioral variables examined was significantly associated with platelet 5-HT levels. **Conclusions:** The platelet hyperserotonemia of autism was replicated in Dutch subjects. Platelet 5-HT levels were also increased in PDD-NOS, while no elevation was seen in MR. Platelet 5-HT levels

appeared to be bimodally distributed in the PDD group, with an apparent hyperserotonemic subgroup.

Nair-Miranda, K., A. Murch, et al. (2004). "An investigation into sub-telomeric deletions of chromosome 22 and pervasive developmental disorders." *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics*, 125B(1), 99-104.

Deletions of the sub-telomeric region of chromosome 22 have been associated with mental retardation, developmental delay, and autistic behaviors. This study investigated sub-telomeric anomalies of chromosome 22 using fluorescent in situ hybridization (FISH) probes in 82 subjects diagnosed with autism and atypical autism. No microdeletions were detected in this group. Similar FISH analyses were undertaken on two children with developmental delay, who were ascertained to be ring 22 during routine cytogenetic investigations. One subject was shown to have a microdeletion in the sub-telomeric region tested. Both children met the social and communication cut off for autism on the ADI and but did not meet the cut off for restrictive and repetitive behaviors. Only one of the two children met the criteria for PDD on the ADOS. (C) 2003 Wiley-Liss, Inc.

Ozonoff, S., I. Cook, et al. (2004). "Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: Evidence from the Collaborative Programs of Excellence in Autism Network." *Journal of Autism and Developmental Disorders*, 34(2), 139-150.

Recent structural and functional imaging work, as well as neuropathology and neuropsychology studies, provide strong empirical support for the involvement of frontal cortex in autism. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computer-administered set of neuropsychological tests developed to examine specific components of cognition. Previous studies document the role of frontal cortex in performance of two CANTAB subtests: the Stockings of Cambridge, a planning task, and the Intradimensional/Extradimensional Shift task, a measure of cognitive set shifting. To examine the integrity of frontal functions, these subtests were administered to 79 participants with autism and 70 typical controls recruited from seven universities who are part of the Collaborative Programs of Excellence in Autism network. The two groups were matched on age, sex, and full-scale IQ. Significant group differences were found in performance on both subtests, with the autism group showing deficits in planning efficiency and extradimensional shifting relative to controls. Deficits were found in both lower- and higher-IQ individuals with autism across the age range of 6 to 47 years. Impairment on the CANTAB executive function subtests did not predict autism severity or specific autism symptoms (as measured by the ADI-R and ADOS), but it was correlated with adaptive behavior. If these CANTAB subtests do indeed measure prefrontal function, as suggested by previous research with animals and lesion patients, this adds to the accumulating evidence of frontal involvement in autism and indicates that this brain region should remain an active area of investigation.

Paul, R., S. Miles, et al. (2004). "Adaptive behavior in autism and Pervasive Developmental Disorder-Not Otherwise Specified: Microanalysis of scores on the

Vineland Adaptive Behavior Scales." *Journal of Autism and Developmental Disorders*, 34(2), 223-228.

The purpose of this study is to provide a microanalysis of differences in adaptive functioning seen between well-matched groups of school-aged children with autism and those diagnosed as having Pervasive Developmental Disorder-Not Otherwise Specified, all of whom functioned in the mild to moderate range of intellectual impairment. Findings indicate that the major area of difference between children with autism and those with Pervasive Developmental Disorder-Not Otherwise Specified, was expressive communication; specifically, the use of elaborations in syntax and morphology and in pragmatic use of language to convey and to seek information in discourse. Linear discriminant function analysis revealed that scores on just three of these expressive communication item sets correctly identified subjects in the two diagnostic categories with 80% overall accuracy. Implications of these findings for both diagnosis and intervention with children with Autism Spectrum Disorders will be discussed.

Robel, L., K. Ennouri, et al. (2004). Discrimination of face identities and expressions in children with autism: same or different? *European Child & Adolescent Psychiatry* 13(4) 227-233.

Autism is a pervasive developmental disorder (PDD) characterized by the association of communication and socialization impairments, and by repetitive stereotyped behaviours. The Minnesota Test of Affective Processing (MNTAP) was used to investigate the discrimination of face identities and face expressions by autistic children. Young children in the 6- to 10-year-old age range suffering from PDD were compared to paired normal children. When the expressions on faces remained neutral, autistic patients had more difficulty in distinguishing different faces than in matching the same facial identities in face pairs: they perceived different faces as being identical. However, recognition errors disappeared when expressions were changed together with face identity. When autistic children were asked to distinguish expressions, they discriminated better identity than difference, just as normal children do. Analysis of face and expression discrimination in terms of identity and difference is a novel approach for the understanding of the clinical features of autism. Autistic children seek sameness and use an atypical strategy to analyse human faces and expressions.

Seltzer, M. M., Shattuck, P., Abbeduto, L., & Greenberg, J. S. (2004). Trajectory of development in adolescents and adults with autism. *Mental Retardation and Developmental Disabilities Research Reviews*, 10(4), 234-247.

This article seeks to elucidate the trajectory of development in adolescents and adults with autism. Prospective, retrospective, and cross-sectional studies are reviewed to reveal the manifestation of and changes in the core symptoms of autism in adolescence and adulthood. Comparing children with adolescents and adults, modest degrees of symptom abatement and improvement in skills have been documented in multiple studies, as are increases in verbal and decreases in performance IQ. Nevertheless, most individuals do not attain normative outcomes in adulthood and continue to manifest significant degrees of symptomatology and dependency. However, a small sub-group (about 15%) has more favorable adult outcomes.

Skovgaard, A. M., Houmann, T., Landorph, S. L., & Christiansen, E. (2004). Assessment and classification of psychopathology in epidemiological research of children 0-3 years of age - A review of the literature. *European Child & Adolescent Psychiatry*, 13(6), 337-346.

The research of psychopathology in children 0-3 years of age is dominated by clinical case studies and theoretical reflections, and epidemiological studies are few. This paper reviews methods to assess and classify psychopathology in children 0-3 years old in an epidemiological context. Diagnostic assessments of children 0-3 years of age are based on information from different sources and investigation of several domains of mental functioning, and the rapid developmental changes and the relationship context are taken into account. The reviewed literature shows a range of methods to assess and classify psychopathology in children 0-3 years of age: screening instruments with established psychometric properties, such as the Child Behaviour Checklist (CBCL) and the Checklist for Autism in Toddlers (CHAT), and methods of in-depth assessment known from both clinical practice and research: developmental tests, such as the Bayley Scales, and relationship assessments, such as the Ear! ly Relational Assessment (ERA). The classification of psychopathology in young children can be approved by the Diagnostic Classification 0-3. The reliability and validity of DC 0-3 have not yet been established, but preliminary results seem promising. The demands made on diagnostic assessment procedures in epidemiological research of children 0-3 years of age can be met by a combination of well-established research instruments, such as the CBCL, with in-depth clinical assessment procedures, such as the Bayley Scales and the ERA, and diagnostic classification by DC 0-3.

Skuse, D., R. Warrington, et al. (2004). "The developmental, dimensional and diagnostic interview (3di): A novel computerized assessment for autism spectrum disorders." *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(5), 548-558.

Objective: Autism is a diagnostic spectrum of variable severity, with significant comorbidity. No existing standardized interview measures autistic features dimensionally. The authors aimed to develop a parental autism interview that could be administered to unselected clinical and general population samples that measures both symptom intensity and comorbidity across the full range of the autistic spectrum. Method: A computerized procedure was devised for administration by trained interviewers that generates symptom and diagnostic profiles for both autism and non-autistic conditions. Test-retest reliability and interrater reliability were assessed in unselected clinical (n = 50) and nonclinical (n = 30) populations. Concurrent validity (n = 120), discriminant validity (n = 120), and criterion validity (n = 29) were evaluated in autistic spectrum and non-autistic patients. Results: Test-retest and interrater reliabilities were excellent (most intraclass correlation coefficients > 0.9). Concurrent validity (agreement with independent clinician formulation) was very good (mean kappa = 0.74). Criterion validity, a comparison with the Autism Diagnostic Interview, was excellent. Discrimination between autistic spectrum versus non-autistic subjects was almost perfect (sensitivity 1.0; specificity > 0.97). Conclusions: The Developmental, Dimensional and Diagnostic Interview (3di) provides an efficient and accurate means of assessing, in dimensional terms, the presence of autistic symptoms in both clinical and normal

populations. It offers novel opportunities for those engaged in research and clinical practice.

Taber, K. H., J. B. Shaw, et al. (2004). "Accentuated Virchow-Robin spaces in the centrum semiovale in children with autistic disorder." *Journal of Computer Assisted Tomography*, 28(2), 263-268.

Objective: The purpose of this study was to assess the incidence of abnormal Virchow-Robin (VR) spaces in children and adolescents with an autistic disorder (AD). An increased incidence of enlarged VR spaces in children has been reported in several developmental disorders. Methods: Sixteen children and adolescents (13 male, 3 female; mean age = 143.5 months; mean IQ = 95.1) with an AD, verified by use of standardized procedures (Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule-Revised), received cranial magnetic resonance (MR) imaging. Sixteen children and adolescents (13 male, 3 female; mean age 160.7 months; mean IQ = 111.6) without AD, as determined using the same procedures, were scanned as a comparison group. The MR scans were performed using a 1.5-T scanner. Two T1-weighted spoiled GRASS sequences (0.7-mm coronal thin-slice, 0-mm gap; 1.5-mm sagittal, 0-mm gap) and a complementary T2-weighted fast spin echo sequence (1.5-mm, 0-mm gap) were obtained. A neuroradiologist and a neurobiologist without clinical information determined the incidence of normal, accentuated, and/or dilated VR spaces. Results: Seven of 16 subjects with AD (approximately 44%) had dilated VR spaces in the centrum semiovale. No grossly abnormal spaces were present in the control subjects. Conclusion: Unusually large VR spaces are seen in at most 22% to 27% of MR scans in children with tension headaches and other psychiatric disorders, suggesting that the incidence of spaces of this type is greater in AD than in other abnormal populations. The origin and significance of this phenomenon remain unknown.

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Baieli, S., L. Pavone, et al. (2003). "Autism and phenylketonuria." *Journal of Autism and Developmental Disorders*, 33(2), 201-204.

Phenylketonuria (PKU) has been also reported in children with infantile autism (IA); however, the frequency of this association is variably reported. Patients with various forms of hyperphenylalaninemia (HPA) were evaluated applying two methods: the Autism Diagnostic Interview-Revised (ADI-R) and the Childhood Autism Rating Scale (CARS). A total of 243 patients were investigated, 97 with classical PKU, 62 identified by neonatal screening, and 35 late diagnosed. None out of 62 patients with classic PKU diagnosed early met criteria for autism. In the group of 35 patients diagnosed late, two boys (5.71%) ages 16 and 13 years fulfilled the diagnostic criteria for autism. The present study confirms that classical PKU is one of the causes of autism, but the prevalence seems to be very low.

Bryson, S. E., Rogers, S. J., & Fombonne, E. (2003). Autism spectrum disorders: Early detection, intervention, education, and psychopharmacological management. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie*, 48(8), 506-516.

Our understanding and treatment of children with autism have changed dramatically since Leo Kanner first formally documented the disorder in 1943. With reference to the historical context, this paper reviews recent research addressing 4 major issues: early detection, intervention, education, and psychopharmacological management of children with autism and related (autistic) spectrum disorders (hereafter, "autism"). We conclude from our review of the evidence that, in the absence of additional, more compelling data, the clinical usefulness of existing screening instruments remains questionable. However, the potential importance of such research is underscored by the clear benefits of early behavioural intervention: despite differences in orientation, outcomes for children with autism can be significantly enhanced with early intensive intervention. Although many questions remain (notably, What are the critical therapeutic components? For whom? For what domains of development? For what level of intensity and duration?), interventions shown to be effective are all carefully planned, engineered, monitored, and designed to target specific skill domains. Including children with autism in regular classes within the public school system poses several challenges, the most pressing of which is the large number of school personnel who need to be trained in evidence-based teaching and behavioural management practices. Finally, psychotropic drugs may help to reduce some symptoms, but they are neither curative nor a substitute for other forms of support and intervention.

Cohen, I. L. (2003). "Criterion-related validity of the PDD behavior inventory." *Journal of Autism and Developmental Disorders*, 33(1), 47-53.

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.

Constantino, J. N., S. A. Davis, et al. (2003). "Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the autism diagnostic interview-revised." *Journal of Autism and Developmental Disorders*, 33(4), 427-433.

Studies of the broader autism phenotype, and of subtle changes in autism symptoms over time, have been compromised by a lack of established quantitative assessment tools. The Social Responsiveness Scale (SRS-formerly known as the Social Reciprocity Scale) is a new instrument that can be completed by parents and/or teachers in 15-20 minutes. We compared the SRS with the Autism Diagnostic Interview-Revised (ADI-R) in 61 child psychiatric patients. Correlations between SRS scores and ADI-R

algorithm scores for DSM-IV criterion sets were on the order of 0.7. SRS scores were unrelated to I.Q. and exhibited inter-rater reliability on the order of 0.8. The SRS is a valid quantitative measure of autistic traits, feasible for use in clinical settings and for large-scale research studies of autism spectrum conditions.

Cuccaro, M. L., Y. J. Shao, et al. (2003). "Behavioral comparisons in autistic individuals from multiplex and singleton families." *Journal of Autism and Developmental Disorders*, 33(1), 87-91.

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, greater than or equal to 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 suggests the possibility that common etiologic mechanisms, either genetic and/or environmental, could underlie all of AD.

Cuccaro, M. L., Y. J. Shao, et al. (2003). "Factor analysis of restricted and repetitive behaviors in autism using the Autism Diagnostic Interview-R." *Child Psychiatry & Human Development*, 34(1), 3-17.

The current study examined the factor structure of restricted and repetitive behaviors (RRB) in children with autism. Factor extraction procedures of 12 items from the Autism Diagnostic Interview-Revised (ADI-R) were applied in N = 207 individuals with autism. Two interpretable factors were identified: Factor 1-repetitive sensory motor actions and Factor 2-resistance to change. There was a significant negative correlation between an index of level of adaptive functioning and Factor 1. Intraclass correlations were not significant for either factor in a subset of families with two or more siblings with autism (multiplex). No differences in scores were apparent for either factor when multiplex families and families containing only one affected individual with autism (singleton) were compared. RRB in autism are represented by two distinct factors which may reflect two separate groups within autism. Defining subgroups within autism will allow for reduction of clinical heterogeneity and enhance our ability to dissect the genetic etiology of this complex disorder.

Fecteau, S., L. Mottron, et al. (2003). "Developmental changes of autistic symptoms." *Autism*, 7(3), 255-268.

The study examined developmental changes in autistic symptoms retrospectively in a sample of 28 verbal children and adolescents with autism. Individuals with Asperger syndrome, PDD-NOS, and related medical conditions were not included in the study. We compared autistic symptoms present at the retrospective assessment and during the 4- to 5-year age period using the ADI-R. Our findings revealed a significant improvement in the three domains relevant for the diagnosis of autism, independent of age or IQ level. Improvement occurred in more symptoms from the social than the communication domain, and for more symptoms from the latter than the restricted interest and repetitive behavior domains. The finding that improvement was not linked to level of functioning and was found in individuals still positive for a diagnosis of autism suggests that improvement belongs to the 'natural history' of the handicap.

Herman, K., S. Nowicki, et al. (2003). "Correlations between DNA, FMRP, and mRNA levels and ADOS-G and ADI-R scores in patients with Fragile X Syndrome." *American Journal of Human Genetics*, 73(5), 330-330.

Hollander, E., A. King, et al. (2003). "Obsessive-compulsive behaviors in parents of multiplex autism families." *Psychiatry Research*, 117(1), 11-16.

Parents of autistic probands with high and low rates of repetitive behaviors were compared for rates of obsessive-compulsive traits and disorder. The rate of repetitive behaviors was assessed using the Autism Diagnostic Interview-Revised (ADI-R) in 176 autistic probands from 57 multiplex families. Obsessive-compulsive disorder (OCD) in parents was determined by direct interview using a parental history questionnaire, with screening for obsessive-compulsive traits using the Yale-Brown Obsessive-Compulsive Scale checklist. Children who had high total scores on the repetitive behavior domain of the ADI-R were significantly more likely to have one or both parents with obsessive-compulsive traits or disorder compared with children who had low total scores on this domain. Children with high scores on D1/D2 of the ADI-R (narrow restricted interests and rituals) were significantly more likely to have one or both parents with OCD, especially fathers, than those with low D1/D2. The occurrence of obsessive-compulsive traits or disorder in parents of autistic children in multiplex families is significantly more likely if autistic children have a high occurrence of repetitive behaviors. Dichotomizing autistic probands by severity and type of repetitive behaviors (circumscribed interests and compulsive rituals) may yield more homogenous groups, which could be helpful in genetic linkage studies. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

Howlin, P. (2003). "Outcome in high-functioning adults with autism with and without early language delays: Implications for the differentiation between autism and Asperger syndrome." *Journal of Autism and Developmental Disorders*, 33(1), 3-13.

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.

Kabot, S., W. Masi, et al. (2003). "Advances in the diagnosis and treatment of autism spectrum disorders." *Professional Psychology-Research and Practice*, 34(1), 26-33.

A dramatic increase in the number of children who are diagnosed with an autistic disorder has given rise to a deluge of articles on autism in the professional as well as the popular literature. This review of the current literature Summarizes and synthesizes recent information on the causes and manifestations of autism, the trends in screening, diagnosis, and assessment; and the salient features of different treatment programs. It provides an overview of the advances and controversial issues that are of special interest to practicing clinical psychologists.

Kulisek, R., M. Hrdlicka, et al. (2003). "Simultaneous occurrence of epilepsy worsens some symptoms of autistic spectrum disorders." *Ceskoslovenska Psychologie*, 47(2), 97-104.

The aim of the study was to clarify the relation of occurrence of epilepsy to autistic psychopathology. The sample of 77 patients of autistic spectrum was examined (61 boys, 16 girls) with average age of 9.1 + 5.3 years. The observation scale CARS, semi-structured interview ADI-R, Stanford-Binet intelligence test, and Gessel's developmental scale were used in the examination. The clinical neurological examination included the EEG examination, too. 79.7 % of patients in the sample were mentally retarded. Epilepsy was found in 17 patients (22.1 %). The total mean score in CARS was 37.3 + 6.7 and it did not correlate significantly with the occurrence of epilepsy. The epilepsy was correlated significantly positively to CARS scale items number 2 ("imitation", $p < 0.001$) and 7 ("visual response", $p < 0.001$) and to subscales of ADI-R questionnaire "lack of shared enjoyment" ($p = 0.02$), "inability to compensate the missing speech by gestures" ($p = 0.006$), and "lack of spontaneous symbolic or social imitative play" ($p = 0.012$). The results prove that simultaneous occurrence of epilepsy worsens some symptoms of pervasive developmental disorders.

Nurmi, E. L., M. Dowd, et al. (2003). "Exploratory subsetting of autism families based on savant skills improves evidence of genetic linkage to 15q11-q13." *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(7), 856-863.

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.

Rogers, S.J., Hepburn, S., & Wehner, E. (2003). Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *Journal of Autism and Developmental Disorders*, 33 (6), 631-642

The Short Sensory Profile was used to assess parental report of sensory reactivity across four groups of young children ($n = 102$). Groups were autism ($n = 26$), fragile X syndrome ($n = 20$), developmental disabilities of mixed etiology ($n = 32$), and typically developing children ($n = 24$). Groups were comparable on overall mental age ($x = 22$ months), and clinical groups were comparable on chronological age ($x = 31$ months). Significant differences were detected at $\alpha < .01$ for tactile sensitivity [$F(3,99) = 10.01$], taste/smell sensitivity [$F(3,99) = 11.63$], underreactive/seeking stimulation [$F(3,99) = 4.56$], auditory filtering [$F(3,99) = 19.67$], and low energy/weak muscles [$F(3,99) = 14.21$]. Both children with fragile X syndrome and children with autism had significantly more sensory symptoms overall than the two comparison groups, and children with autism did not differ significantly from children with fragile X syndrome. Both groups were more impaired than developmentally delayed and typically developing children in tactile sensitivity and auditory filtering. Children with autism were more abnormal in responses to taste and smell than all other groups. Children with fragile X syndrome were more abnormal than all other groups in low energy/weak muscles. Sensory reactivity of children with developmental delays was comparable to mental age-matched typically developing toddlers. Correlational analyses indicated that neither overall developmental level nor IQ was related to abnormal sensory reactivity in children with autism or general developmental disorders. However, abnormal sensory reactivity had a significant relationship with overall adaptive behavior.

Shao, Y. J., M. L. Cuccaro, et al. (2003). "Fine mapping of Autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes." *American Journal of Human Genetics*, 72(3), 539-548.

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.

Starr, E., P. Szatmari, et al. (2003). "Stability and change among high-functioning children with pervasive developmental disorders: A 2-year outcome study." *Journal of Autism and Developmental Disorders*, 33(1), 15-22.

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.

Tidmarsh, L., & Volkmar, F. R. (2003). Diagnosis and epidemiology of autism spectrum disorders. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie*, 48(8), 517-525.

In this paper, we give an overview of the diagnostic categories of autism and other pervasive developmental disorders (PDDs) and discuss the changes in the DSM classification system over the past 20 years. We describe each subtype of PDD, along

with comorbid psychiatric conditions, assessment guidelines, and tools for diagnosis. The epidemiology of autism has generated much discussion and research; we report the most recent data, as well as recent findings about controversial issues purporting to cause the increased prevalence rate observed in the past decade. Finally, we discuss the prognosis for individuals with autism, indicating the challenges faced by patients, families, and professionals aiming to optimize their outcome.

Tomblin, J. B., L. L. Hafeman, et al. (2003). "Autism and autism risk in siblings of children with specific language impairment." *International Journal of Language & Communication Disorders*, 38(3), 235-250.

Background: Several studies have shown that family members of children with autism have elevated rates of spoken and written speech and language problems. Aims: This study asked whether there was also a greater rate of siblings with autism among probands with specific language impairment. Methods & Procedures: The probands in this study were 158 children with specific language impairment and 132 children with normal language status. These probands had 522 siblings who were examined for risk of autism using the Autism Behavior Checklist. Siblings found to be at risk were then examined using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-G. Outcomes & Results: A concentration of siblings with risk for a diagnosis of autism was found in association with probands who had poor spoken language skills. Four siblings of the 522 (0.8%) met the diagnostic standards for autism. All the probands of these siblings had spoken language scores below -1 SD and three had diagnoses of spoken language impairment. Conclusions: These data provide additional support for a familial association between autism and spoken language impairment.

Published 2002

Alarcon, M., R. M. Cantor, et al. (2002). "Evidence for a language quantitative trait locus on chromosome 7q in multiplex autism families." *American Journal of Human Genetics*, 70(1), 60-71.

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 behavior." 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 ($Z = 2.85$ $P = .002$ $\chi^2(2) = 18.84$, $df = 8$, $P = .016$). Moreover, the peak fine-mapping result for repetitive behavior ($Z = 2.48$; $P = .007$) 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.

Silverman, J. M., C. J. Smith, et al. (2002). "Symptom domains in autism and related conditions: Evidence for familiarity." *American Journal of Medical Genetics*, 114(1), 64-73.

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 sibships. The variance within sibships 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 sibships (cases: n = 289; sibships: 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 sibships 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. (C) 2001 Wiley-Liss, Inc.

Spiker, D., L. J. Lotspeich, et al. (2002). "Behavioral phenotypic variation in autism multiplex families: Evidence for a continuous severity gradient." *American Journal of Medical Genetics*, 114(2), 129-136.

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. (C) 2002 Wiley-Liss, Inc.

Szatmari, P., C. Merette, et al. (2002). "Quantifying dimensions in autism: A factor-analytic study." *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(4), 467-474.

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.

Vrancic, D., V. Nanclares, et al. (2002). "Sensitivity and specificity of the autism diagnostic inventory-telephone screening in Spanish." *Journal of Autism and Developmental Disorders*, 32(4), 313-320.

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.

Zhang, H., X. Liu, et al. (2002). "Reelin gene alleles and susceptibility to autism spectrum disorders." *Molecular Psychiatry*, 7(9), 1012-1017.

A polymorphic trinucleotide repeat (CGG/GCC) within the human Reelin gene (RELN) was examined as a candidate gene for autism spectrum disorders (ASDs). This

gene encodes a large extracellular matrix protein that orchestrates neuronal positioning during corticogenesis. The CGG-repeat within the 5' untranslated region of RELN exon 1 was examined in 126 multiple-incidence families. The number of CGG repeats varied from three to 16 in affected individuals and controls, with no expansion or contraction observed during maternal (n = 291) or paternal (n = 287) transmissions in families with autistic probands. Although the frequencies of the RELN alleles and genotypes in affected children were not different from those in the comparison group, a family-based association test (FBAT) showed that the larger RELN alleles (greater than or equal to 11 repeats) were transmitted more often than expected to affected children (S = 43, E(S) = 34.5, P = 0.035); this was particularly the case for the 13-repeat RELN allele (S = 22, E(S) = 16, P = 0.034). Affected sib-pair (ASP) analysis found no evidence of excess sharing of RELN alleles in affected siblings. The impact of genotypes with large alleles (greater than or equal to 11 repeats) on the phenotypes in individuals with ASD was analyzed by ANOVA in a subset of the families for which results of the Autism Diagnostic Interview-Revised were available. Children with large RELN alleles did not show any difference in scores for questions related to the core symptoms of autistic disorder, but there was a tendency for children with at least one large RELN allele to have an earlier age at first phrase ($\chi^2 = 3.538$, P = 0.06). Thus, although the case-control and affected sib-pair findings did not support a role for RELN in susceptibility to ASD, the more powerful family-based association study demonstrated that RELN alleles with larger numbers of CGG repeats may play a role in the etiology of some cases of ASD, especially in children without delayed phrase speech.

Published 2001

Abramson, R. K., M. L. Cuccaro, et al. (2001). "Comparison of the autism diagnostic interview-revised (ADI) restrictive/repetitive behaviors and the aberrant behavior checklist (ABC) stereotypy scores." *American Journal of Human Genetics*, 69(4), 284-284.

Asano, E., D. C. Chugani, et al. (2001). "Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction." *Neurology* 57(7): 1269-1277.

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-[F-18]fluoro-D-glucose (FDG) and alpha-[C-11]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 greater than or equal to 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 neocortices 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.

Bolte, S. and F. Poustka (2001). "The factor structure of the Autism Diagnostic Interview-Revised (ADI-R): A study on the dimensional versus the categorical classification of autistic disorders." *Zeitschrift Fur Kinder-Und Jugendpsychiatrie Und Psychotherapie*, 29(3), 221-229.

Objectives: This study investigated whether empirically derived dimensions of autistic behavior are consistent with the content-valid construction of the autistic behavior domains according to ICD-10 and DSM-IV (social interaction, communication and repetitive, stereotyped behavior). Methods: A principal component exploratory factor analysis routine with varimax-rotation and extraction of factors following the Scree criterion was run using data from the Autism Diagnostic Interview-Revised (ADI-R) of N = 262 individuals exhibiting autism or autistic features. Results: A three-factor solution consisting of two socio-communicative and one language dimension and accounting for 46.1% of the total variance was found to best describe the data. These factors yielded only vague correspondence with the idea of behavior domains described in ICD-10 and DSM-IV. In addition, factor loadings of items representing repetitive, stereotyped patterns were generally weak. Conclusions: The factor-analytic approach to autism indicates a conception of the disorder divergent from that defined in the contemporary psychiatric classification systems, especially regarding the area of repetitive, stereotyped behavior.

Buchsbaum, M. S., E. Hollander, et al. (2001). "Effect of fluoxetine on regional cerebral metabolism in autistic spectrum disorders: a pilot study." *International Journal of Neuropsychopharmacology*, 4(2), 119-125.

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 Asperge's syndrome (n = 1), entered a 16-wk placebo-controlled cross-over trial of fluoxetine. The patients received F-18-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.

Chakrabarti, S. and E. Fombonne (2001). "Pervasive developmental disorders in preschool children." *Jama-Journal of the American Medical Association*, 285(24), 3093-3099.

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 15500 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 10000 children. Prevalences were 16.8 per 10000 for autistic disorder and 45.8 per 10000 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.

Fombonne, E. and S. Chakrabarti (2001). "No evidence for a new variant of measles-mumps-rubella-induced autism." *Pediatrics*, 108(4).

Objective. A link has been postulated between measles-mumps-rubella (MMR) vaccine and a form of autism that is a combination of developmental regression and gastrointestinal symptoms that occur shortly after immunization. This hypothesis has involved 3 separate claims: 1) that there is new phenotype of autism involving regression and gastrointestinal symptoms, 2) that this new variant is responsible for the alleged rise of autism rates, and 3) that this phenotype is associated with biological findings suggestive of the persistence of measles infection. We tested the first of these claims. If this new "autistic enterocolitis" syndrome had some validity, then 1 or several of the following 6 predictions should be supported by empirical data: 1) childhood disintegrative disorder has become more frequent, 2) the mean age of first parental concern for autistic children who are exposed to MMR is closer to the mean immunization age than in children who are not exposed to MMR, 3) regression in the development of children with autism has become more common in MMR-vaccinated children, 4) the age of onset for autistic children with regression clusters around the MMR immunization date and is different from that of autistic children without regression, 5) children with regressive autism have distinct symptom and severity profiles, and 6) regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder. Methods. Three samples were used. Epidemiologic data on 96 children (95 immunized with MMR at a median age of 13.5 months) who were born

between 1992 and 1995 and had a pervasive developmental disorder diagnosis as reported in a recent UK survey (post-MMR sample) were compared with data from 2 previous clinical samples (1 pre-MMR [n = 98] and 1 post-MMR [n = 68]) of autistic patients. All patients were assessed with the standardized Autism Diagnostic Interview (ADI), allowing rigorous comparison of age at first parental concerns and rates of regression across samples. Reliability was excellent on ADI scores, age of parental concern, and developmental regression. Furthermore, data on bowel symptoms and disorders were available in the epidemiologic survey from both pediatric and parental sources, and immunization dates were obtained from computerized records. Results. The prevalence of childhood disintegrative disorder was 0.6/10000 (95% confidence interval: 0.02-3.6/10000); this very low rate is consistent with previous estimates and is not suggestive of an increased frequency of this form of pervasive developmental disorder in samples of children who are immunized with MMR. There was no difference in the mean age at first parental concern between the 2 samples exposed to MMR (19.3 and 19.2 months) and the pre-MMR sample (19.5 months). Thus, MMR immunization was not associated with a shift toward an earlier age for first parental concerns. Similarly, the rate of developmental regression reported in the post-MMR sample (15.6%) was not different from that in the pre-MMR sample (18.4%); therefore, there was no suggestion that regression in the developmental course of autism had increased in frequency since MMR was introduced. In the epidemiologic sample, the subset of autistic children with regression had no other developmental or clinical characteristics, which would have argued for a specific, etiologically distinct phenotype. Parents of autistic children with developmental regression detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months). Moreover, the mean intervals from MMR immunization to parental recognition of autistic symptoms were comparable in autistic children with or without regression (248 vs 272 days; not significant). In the epidemiologic sample, gastrointestinal symptoms were reported in 18.8% of children. Constipation was the most common symptom (9.4%), and no inflammatory bowel disorder was reported. Furthermore, there was no association between developmental regression and gastrointestinal symptoms (odds ratio: 0.63;

Gilchrist, A., J. Green, et al. (2001). "Development and current functioning in adolescents with Asperger syndrome: A comparative study." *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 42(2), 227-240.

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 WFA group, but relatively good performance on the Block Design subtest of the WLSC/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.

Hill, A., S. Bolte, et al. (2001). "Stability and interpersonal agreement of the interview-based diagnosis of autism." *Psychopathology*, 34(4), 187-191.

Interpersonal agreement and stability of the Autism Diagnostic Interview-Revised (ADI-R) was examined in this study. Four raters judging 55 subjects agreed moderately to excellently on the items of the diagnostic algorithm, operationalizing the main autistic symptoms according to the classification guidelines of ICD-10 and DSM-IV. When retesting 33 individuals, some items revealed only weak stability. On the level of domains of autistic behavior and diagnosis, the interrater reliability and retest reliability were consistently convincing. Copyright (C) 2001 S. Karger AG, Basel.

Juul-Dam, N., J. Townsend, et al. (2001). "Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population." *Pediatrics*, 107(4).

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.

King, B. H., D. M. Wright, et al. (2001). "Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder." *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(6), 658-665.

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.

Lord, C., B. L. Leventhal, et al. (2001). "Quantifying the phenotype in autism spectrum disorders." *American Journal of Medical Genetics*, 105(1), 36-38.

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. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 105:36-38, 2001, (C) 2001 Wiley-Liss, Inc.

Magnusson, P. and E. Saemundsen (2001). "Prevalence of autism in Iceland." *Journal of Autism and Developmental Disorders*, 31(2), 153-163.

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.

Mildenberger, K., S. Sitter, et al. (2001). "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." *European Child & Adolescent Psychiatry*, 10(4), 248-255.

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 behavioural features at pre-school age (age range 4-5 years) were better suited to differentiate the groups than the items reflecting behavioural features at the time of the investigation (mean age: 9 years). The items on the dimension "Reciprocal social interaction" and "Communication and language" discriminated the groups better than the items of the dimension "Restricted interests". 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.

Rutter, M. L., J. M. Kreppner, et al. (2001). "Specificity and heterogeneity in children's responses to profound institutional privation." *British Journal of Psychiatry*, 179, 97-103.

Declaration of interest: The research was supported by funds from the Department of Health, the Medical Research Council and the Helmut Horten Foundation. *Background:* The sequelae of profound early privation are varied. *Aims:* To delineate the behavioural patterns that are specifically associated with institutional privation. *Method:* A group of 165 children adopted from Romania before the age of 42 months were compared at 4 years and 6 years with 52 non-deprived UK children adopted in infancy. Dysfunction was assessed for seven domains of functioning. The groups were compared on which, and how many, domains were impaired. *Results:* Attachment problems, inattention/overactivity, quasi-autistic features and cognitive impairment were associated with institutional privation, but emotional difficulties, poor peer relationships and conduct problems were not. Nevertheless, one-fifth of children who spent the longest time in institutions showed normal functioning. *Conclusions:* Attachment disorder behaviours, inattention/overactivity and quasi-autistic behaviour constitute institutional privation patterns.

Starr, E., S. K. Berument, et al. (2001). "A family genetic study of autism associated with profound mental retardation." *Journal of Autism and Developmental Disorders*, 31(1), 89-96.

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-IO 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.

Rogers, S. J., Wehner, E. A., & Hagerman, R. (2001). The behavioral phenotype in fragile X: Symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioral Pediatrics*, 22(6), 409-417.

Explored the behavioral phenotype of autism in a group of young children with *fragile X* syndrome (FXS). The authors compared 24 children with FXS with 2 well-matched groups: 27 children with autism (AD) and 23 children with other developmental delays (DD), on 2 standardized autism instruments, as well as on measures of development and adaptive behavior. All children were aged between 21-48 months. 2 FXS subgroups emerged, one of which did not meet study criteria for autism (16 Ss). Their profiles on the autism instruments and the developmental instruments were virtually identical to the other DD group. The other FXS subgroup (8 Ss, or 33% of the total FXS group) met study criteria for autism. Their profiles on the autism instruments were virtually identical to the group with autism. The finding of 2 FXS subgroups raises a

hypothesis of additional genetic influences in the FXS autism group, warranting further genetic studies.

Tierney, E., N. A. Nwokoro, et al. (2001). "Behavior phenotype in the RSH/Smith-Lemli-Opitz syndrome." *American Journal of Medical Genetics*, 98(2), 191-200.

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. (C) 2001 Wiley-Liss, Inc.

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Arnold, L. E., M. G. Aman, et al. (2000). "Assessment in multisite randomized clinical trials of patients with autistic disorder: The autism RUPP network." *Journal of Autism and Developmental Disorders*, 30(2), 99-111.

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.

Bolte, S., K. Crecelius, et al. (2000). "The Questionnaire on Behaviour and Social Communication (VSK): An autism screening instrument for research and practice." *Diagnostica*, 46(3), 149-155.

The psychometric properties of the Questionnaire on Behaviour and Social Communication (VSK), a German adaptation of the Autism Screening Questionnaire (ASQ), were investigated in this study. It is a 40-item parent-report instrument derived from the Autism Diagnostic Interview-Revised (ADI-R) to screen for autism. In a sample of 83 subjects showing autism or autistic features the instrument had an internal consistency of $\alpha=.85$, with items mostly being average in difficulty and all item-total correlations exceeding $r=.40$. Stability after an interval of 12-24 months in a small subsample of 17 subjects was $r(ii)=.74$. The convergence with the ADI-R reached $r=.66$. The total score of the questionnaire discriminated highly significantly between 72 autistic subjects, 20 non-autistic/cognitive impaired subjects ($IQ<85$), 26 mixed-clinical subjects and 22 normal controls. A cut-off of 17 had a specificity of 99% and a sensitivity of 92%. Data suggest that the Questionnaire on Behaviour and Social Communication is a valuable tool to generate suspicion of autism For different clinical or research purposes.

Dawson, G., J. Osterling, et al. (2000). "Case study of the development of an infant with autism from birth to two years of age." *Journal of Applied Developmental Psychology*, 21(3), 299-313.

This report describes a case study of the development of an infant with autism who was observed closely by professionals from birth and to whom a comprehensive psychological evaluation was administered at approximately 1 and 2 years of age. During the first 6 months of life I this infant displayed difficulties in oral motor coordination and muscle tone that fluctuated between hypotonia and hypertonia. He startled easily, had poor state regulation, and was hypersensitive to touch. Notably, however, during the first 6 months, this infant vocalized and responded socially to others by smiling and cooing. During the second half of the first year, he continued to demonstrate diffuse sensorimotor difficulties and diminished oral motor control. Hypersensitivity now extended to a wider range of stimuli. He had problems in sleep regulation. Motor stereotypies, including rocking, head banging, and toe walking, were observed. Difficulties in the domain of social interaction began to emerge during the second 6 months, including poor eye contact, failure to engage in imitative games, and lack of imitative vocal responses. By a little over 1 year of age, this infant met diagnostic criteria for autism based on the Autism Diagnostic Interview. There were several domains in which this toddler with autism did not show impairments. In the areas of immediate memory for actions, working memory,

response inhibition, and speech perception, this 1-year old with autism displayed no evidence of significant impairment on the tests administered. This case study offers clues regarding the nature of autism at its earliest stages. Understanding early development in autism will be important for developing early screening and diagnostic tools.

Donnelly, S. L., C. M. Wolpert, et al. (2000). "Female with autistic disorder and monosomy X (Turner syndrome): Parent-of-origin effect of the X chromosome." *American Journal of Medical Genetics*, 96(3), 312-316.

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.

Miller, J. N. and S. Ozonoff (2000). "The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology." *Journal of Abnormal Psychology*, 109(2), 227-38.

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.

Szatmari, P., Bryson, S. E., Streiner, D. L., Wilson, F., Archer, L., & Rye, C. (2000). Two-year outcome of preschool children with autism or Asperger's syndrome. *American Journal of Psychiatry*, 157(12), 1980-1987.

Mental Disorders-IV (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 yrs on variables independent of the defining criteria and to identify variables that might account for these differences. All children 4-6 yrs of age who came for assessment or were currently in treatment at a pervasive developmental disorder service were identified. Results suggest that children with Asperger's syndrome had better social skills and fewer autistic symptoms 2 yrs 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 and follow-up were very similar to the children with Asperger's syndrome at study enrollment.

Tanguay, P. E. (2000). "Pervasive developmental disorders: A 10-year review." *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(9), 1079-1095.

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.

Tierney, E., N. A. Nwokoro, et al. (2000). "Behavioral phenotype of RSH/Smith Lemli-Opitz syndrome." *Mental Retardation and Developmental Disabilities Research Reviews*, 6(2), 131-134.

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. (C) 2000 Wiley-Liss, Inc.

Wolpert, C. M., M. M. Menold, et al. (2000). "Three probands with autistic disorder and isodicentric chromosome 15." *American Journal of Medical Genetics*, 96(3), 365-372.

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. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 96:365-372, 2000. (C) 2000 Wiley-Liss, Inc.

Published 1999

Berument, S. K., M. Rutter, et al. (1999). "Autism screening questionnaire: diagnostic validity." *British Journal of Psychiatry*, 175, 444-451.

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. Declaration of interest The study was supported by the Medical Research Council.

Bolte, S., H. Dickhut, et al. (1999). "Patterns of parent-reported problems indicative in autism." *Psychopathology*, 32(2), 93-97.

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.

Cox, A., K. Klein, et al. (1999). "Autism spectrum disorders at 20 and 42 months of age: Stability of clinical and ADI-R diagnosis." *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 40(5), 719-732.

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.

MacLean, J. E., P. Szatmari, et al. (1999). "Familial factors influence level of functioning in pervasive developmental disorder." *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(6), 746-753.

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 familiar 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 in 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.

Ozonoff, S., B. J. Williams, et al. (1999). "Autism and autistic behavior in Joubert syndrome." *Journal of Child Neurology*, 14(10), 636-641.

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.

Robertson, J. M., P. E. Tanguay, et al. (1999). "Domains of social communication handicap in autism spectrum disorder." *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(6), 738-745.

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.

Published 1998

Baker, P., J. Piven, et al. (1998). "Autism and tuberous sclerosis complex: Prevalence and clinical features." *Journal of Autism and Developmental Disorders*, 28(4), 279-285.

This study employed a hierarchical assessment to detect the prevalence of autism in a clinic sample of individuals with tuberous sclerosis complex (TSC). After screening subjects with the Autism Behavior Checklist, subsequent evaluations with the Autism Diagnostic Interview, and direct clinical observation, the prevalence of autistic disorder in this sample of 20 subjects was conservatively estimated at 20%. Data suggest a possible association between both hypsarrhythmia and TSC-related cardiac abnormalities with autism in this subgroup of TSC individuals. Implications of these findings for clinical practice and further research are discussed.

Davies, M., O. Udwin, et al. (1998). "Adults with Williams syndrome: Preliminary study of social, emotional and behavioural difficulties." *British Journal of Psychiatry*, Vol: 273-276.

Investigated whether a profile of distinctive patterns of behavioral and psychological characteristics can be identified in adults with Williams syndrome. Parents and other care-givers were interviewed about the social, emotional and behavioral characteristics of 70 adults (aged 19-39 yrs) with Williams syndrome, using the Social and Emotional Functioning Interview, the Vineland Adaptive Behaviour Scale, and a number of sections from the Autism Diagnostic Interview. Ss were reported to have high rates of behavioral and emotional difficulties, particularly in terms of poor social relationships, over-friendliness and social disinhibition, preoccupations and obsessions, and high levels of anxiety and distractibility. Findings provide preliminary support for the existence of a specific pattern of behavioral and personality characteristics and associated difficulties in adults with Williams syndrome. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

De Giacomo, A. and E. Fombonne (1998). "Parental recognition of developmental abnormalities in autism." *European Child & Adolescent Psychiatry*, 7(3), 131-136.

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 mo when the parents first became concerned, and the first professional advice was sought when children were 24.1 mo. The most common parental concerns were for speech and language development, followed by abnormal socioemotional 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. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Jambaque, I., L. Mottron, et al. (1998). "Autism and visual agnosia in a child with right occipital lobectomy." *Journal of Neurology Neurosurgery and Psychiatry*, 65(4), 555-560.

Objectives-Autistic disorder is a developmental handicap with an unknown neurological basis. Current neuropsychological models for autism suggest an abnormal construction of visual perceptual representation or a deficit in executive functions. These models predict cerebral lesions in the temporo-occipital or frontal regions of autistic patients. The present study aimed at studying the presence of symptoms of autism and visual agnosia in a 13 year old girl who had a right temporo-occipital cortical dysplasia that was surgically removed at the age of 13. Methods-Neuropsychological evaluation included Wechsler and Kaufman intelligence scales, a test of word fluency, digit span, Corsi block, California verbal learning, Trail making, Benton facial recognition, Snodgrass object recognition tests, Rivermead face learning subtest, and developmental test of visual perception. The ADI-R was used to show current and retrospective diagnosis of autistic disorder. Neuroimaging included brain MRI, single photon emission computed tomography (SPECT), and PET. Results-Brain MRI showed a right occipital defect and an abnormal hyperintensity of the right temporal cortex. PET and SPECT disclosed a left frontal hypometabolism together with the right occipital defect. Neuropsychological testing showed a visual apperceptive agnosia and executive function deficits. Psychiatric study confirmed the diagnosis of autistic disorder. Conclusions-Although the possibility that autism and visual agnosia were dissociable factors in this patient cannot be excluded, the finding of both deficits supports the possibility that occipitotemporal lesions can predispose to the development of autism.

Mahoney, W. J., P. Szatmari, et al. (1998). "Reliability and accuracy of differentiating pervasive developmental disorder subtypes." *Journal of the American Academy of Child & Adolescent Psychiatry*, 37(3), 278-285.

Evaluated the ability of the Mental Disorders-IV (DSM-IV) criteria for the pervasive developmental disorders (PDD) to reliably and accurately differentiate PDD subtypes. The sample consisted of 143 children (mean age 9.4 yrs) with various types of developmental disabilities. A diagnosis of PDD and PDD subtype was made by 1 clinician using information obtained from the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). The raw data from the ADI-R, clinical notes, ADOS, IQ, and other available data were independently assessed by 3 experienced raters, each of whom then made a separate, blind diagnosis. If there was any disagreement, a consensus best-estimate (CBE) diagnosis was made after discussion. The current DSM-IV criteria showed good to excellent reliability for the diagnosis of PDD, Asperger's disorder (AsD), and autism, but they showed poor reliability for the diagnosis of atypical autism. The clinician (compared to the CBE) had little difficulty differentiating PDD from non-PDD children and autism from AsD but had more difficulty identifying children with atypical autism. The latent class analysis also showed that the average error rates of the 3 raters for a differentiation of atypical autism from autism were unacceptably high. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Pilowsky, T., N. Yirmiya, et al. (1998). "The Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale: Differences between diagnostic systems and comparison between genders." *Journal of Autism & Developmental Disorders*, 28(2), 143-151.

Diagnoses for autism based on the Autism Diagnostic Interview-Revised (ADI-R) and the Childhood Autism Rating Scale (CARS) were examined for 83 Ss (aged 1.7-32.3 yrs) with suspected autism. Agreement between systems reached 85.7%. Ss receiving diagnosis of autism based on only one system were significantly younger in age than Ss receiving diagnoses according to both systems. Ss who did not receive diagnosis of autism on the ADI-R had lower chronological and mental ages and lower CARS scores compared to Ss who received diagnosis of autism based on the ADI-R. When 18 females and 18 males were matched to examine possible gender differences, no significant findings were revealed, suggesting that the symptoms of autism according to the ADI-R and CARS do not differ between males and females when matched for chronological and mental ages. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Tanguay, P. E., J. Robertson, et al. (1998). "A dimensional classification of autism spectrum disorder by social communication domains." *Journal of the American Academy of Child & Adolescent Psychiatry*, 37(3), 271-277.

Examines whether "social communication" (SC) could be used to assess severity of symptoms in autism spectrum disorder (ASD). SC refers to the communication of cognitive and emotional information through facial expression, gesture, and prosody and through implicit understanding of pragmatics and of theory of mind. 63 Ss (mean age 6.7 yrs) were evaluated by raters using the Autism Diagnostic Interview-Revised and either the Autism Diagnostic Observation Schedule or the Pre-Linguistic Autism Diagnostic Observation Schedule. Two investigators independently diagnosed autism, Asperger's disorder, or pervasive developmental disorder-not otherwise specified. Items from the Autism Diagnostic Interview-Revised that were judged to represent SC behaviors were factor-analyzed. Three factors were identified: affective reciprocity, joint attention, and theory of mind. Comparing this new classification approach to Mental Disorders-IV (DSM-IV) led to suggestions for possible changes in the latter: (1) vocabulary and grammar deficiencies in autistic persons should be coded under developmental language disorder; (2) the diagnosis of Asperger's disorder may not be needed; and (3) requiring that all persons with ASD have a symptom from the "restrictive, repetitive, and stereotypic" list may need to be reconsidered. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Published 1997-1989

Cianchetti, C. and M. G. Marrosu (1993). "[The analysis of nervous system functions in dysmorphic syndromes]." *Pediatria Medica e Chirurgica*, 15(Suppl 1), 26-28.

The involvement of the C.N.S. in dysmorphic syndromes is very frequent; therefore a systematic analysis of the functions of the nervous system is important in the clinical definition of these syndromes. Besides the morphological aspects, studied by magnetic resonance imaging, investigations should be carried out in the neuroelectrophysiological and neuropsychological fields. For the former, the following

examinations are proposed: EEG in wakefulness and sleep, multimodal evoked potentials (VEP, BAEP, SEP), cortical magnetic stimulation and P300 (P3). For the neuropsychological field, a general intelligence test appropriate to the mental age of the subject (the Wechsler, Terman-Merrill, or Brunet-Lezine scale) and, whenever possible, the following complementary tests: Raven's Progressive Matrices, Bender's and Santucci's graphic tests, go-no go, Goodenough draw-a-person, reading and writing tests, Langeot's scale for development of the logical thinking, sorting test and verbal and spatial memory tests. In some cases, the behaviour should be defined, through Conner's scale for attention deficit-hyperactivity disorders, the Autism Diagnostic Interview, the Adaptive Behaviour Scale and the Brief Psychiatric Rating Scale.

Cianchetti, C., G. Sannio-Fancello, et al. (1991). "Neuropsychological, psychiatric, and physical manifestations in 149 members from 18 fragile X families." *American Journal of Medical Genetics*, 40(2), 234-43.

One hundred forty-nine subjects from 18 families with fragile X [fra(X)] syndrome were evaluated for their neuropsychological, psychiatric, and physical characteristics. The 36 fra(X) males had intelligence quotients ranging from less than 20 to 61, which prevented the delineation of a reliable neuropsychological profile. Behaviour fitted DSM-III-R and ADI diagnostic criteria of autism in only 2 subjects, both with very low intelligence level (IQ less than 20). Of 36 heterozygotes (HZ), 22 had an IQ between 20 and 80 and 14 between 81 and 99. The neuropsychological profile of the latter was compared with IQ-age-environment-matched 14 normal females and 14 normal males. Significantly poorer results in HZ were found on immediate digit memory and on Raven's progressive matrices (a visuo-spatial test of logical capabilities). The latter result, in conjunction with those results on the Bender visual-motor gestalt test and on some WAIS subtests, suggests a frequent deficit in spatial capabilities in such subjects. Such results tended to be confirmed by the profiles of the 22 HZ with IQ 20-80. No psychiatric abnormalities were found in HZ, except in one subject with IQ less than 20 which fitted DSM-III-R and ADI criteria for autism. Typical physical manifestations, especially cranio-facial, were more frequently present in the HZ group with lower IQ. Subnormal IQ was probably the most reliable abnormality for the detection of HZ in 49 females at 50% and 25% risk of heterozygosity.

Fombonne, E. (1992). "Diagnostic assessment in a sample of autistic and developmentally impaired adolescents." *Journal of Autism & Developmental Disorders*, 22(4), 563-581.

A sample of 43 autistic and developmentally impaired adolescents were assessed with the Autism Diagnostic Interview (ADI), DSM-III-R criteria, and the clinician's diagnosis. DSM-III-R criteria for autism have low specificity and agree poorly with the other two definitions. Detailed results of the ADI are provided that confirm the usefulness and discriminant validity of this semi-structured diagnostic interview in a sample of very retarded autistic subjects.

Klauck, S. M., E. Munstermann, et al. (1997). "Molecular genetic analysis of the FMR-1 gene in a large collection of autistic patients." *Human Genetics*, 100(2), 224-229.

A genetic etiology in autism is now strongly supported by family and twin studies. A 3:1 ratio of affected males to females suggests the involvement of at least one X-linked locus in the disease. Several reports have indicated an association of the fragile X chromosomal anomaly at Xq27.3 (FRAXA) with autism, whereas others have not supported this finding. We have so far collected blood from 105 simplex and 18 multiplex families and have assessed 141 patients by using the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Scale, and psychometric tests. All four ADI-R algorithm criteria were met by 131 patients (93%), whereas 10 patients (7%) showed a broader phenotype of autism. Southern blot analysis was performed with three different enzymes, and filters were hybridized to an FMR-1-specific probe to detect amplification of the CCG repeat at FRAXA. to the complete FMR-1 cDNA probe. and to additional probes from the neighborhood of the gene. No significant changes were found in 139 patients (99%) from 122 families, other than the normal variations in the population. In the case of one multiplex family with three children showing no dysmorphic features of the fragile X syndrome (one male meeting 3 out of 4 ADI-algorithm criteria, one normal male with slight learning disability but negative ADI-R testing and one fully autistic female), the FRAXA full-mutation-specific CCG-repeat expansion in the genotype was not correlated with the autism phenotype. Further analysis revealed a mosaic pattern of methylation at the FMR-1 gene locus in the two sons of the family, indicating at least a partly functional gene. Therefore, we conclude that the association of autism with fragile X at Xq27.3 is non-existent and exclude this location as a candidate gene region for autism.

Lecouteur, A., M. Rutter, et al. (1989). "Autism Diagnostic Interview - a Standardized Investigator-Based Instrument." *Journal of Autism and Developmental Disorders*, 19(3), 363-387.

The development of a new standardized investigator-based interview for use in the differential diagnosis of pervasive developmental disorders is described, together with a diagnostic algorithm (using ICD-10 criteria) based on its use. Good interrater reliability for algorithm items was shown between four raters, two in Canada and two in the UK, who rated 32 videotaped interviews. The items also significantly discriminated between 16 autistic and 16 nonautistic mentally handicapped subjects. The algorithm based on ICD-10 identified all 16 autistic individuals and none of the 16 nonautistic subjects.

Lord, C., A. Pickles, et al. (1997). "Diagnosing autism: Analyses of data from the autism diagnostic interview." *Journal of Autism and Developmental Disorders*, 27(5), 501-517.

Results from ROC curves of items from two scales, the Autism Diagnostic Interview (ADI) and Autism Diagnostic Interview-Revised (ADI-R), operationalizing DSM-IV criteria for autism are presented for 319 autistic and 113 other subjects from 8 international autism centers. Analyses indicate that multiple items were necessary to attain adequate sensitivity and specificity if samples with varying levels of language were considered separately. Although considering only current behavior was generally sufficient when a combination cutoff and additive model was employed, predictive power was highest when history was taken into account. A single set of criteria, as operationalized when individually structured questions in the ADI/ADI-R, was effective

in differentiating autism from mental handicap and language impairment in subjects with a range of chronological ages and developmental levels.

Lord, C., M. Rutter, et al. (1994). "Autism Diagnostic Interview-Revised - a Revised Version of a Diagnostic Interview for Caregivers of Individuals with Possible Pervasive Developmental Disorders." *Journal of Autism and Developmental Disorders*, 24(5), 659-685.

Describes the Autism Diagnostic Interview-Revised (ADI-R), a revision of the Autism Diagnostic Interview, a semistructured, investigator-based interview for caregivers of children and adults for whom autism or pervasive developmental disorders is a possible diagnosis. The revised interview has been reorganized, shortened, modified to be appropriate for children with mental ages from about 18 months into adulthood and linked to ICD-10 and DSM-IV criteria. Psychometric data are presented for a sample of preschool children.

Lord, C., M. L. Rutter, et al. (1989). "Autism Diagnostic Observation Schedule: A standardized observation of communicative and social behavior." *Journal of Autism & Developmental Disorders*, 19(2), 185-212.

Examined the interrater (IR) and test-retest reliability (TRR) of the Autism Diagnostic Observation Schedule, as well as its concurrent and discriminant validity. 20 autistic and 20 nonautistic, mildly mentally handicapped Ss (aged 6.1-28.8 yrs) with full-scale IQs between 45 and 85 were examined by 5 raters to assess IR and TRR. Further analyses compared these 2 groups with 2 samples of 20 autistic and 20 normal Ss (aged 6.2-28.1 yrs) with normal intelligence (full-scale IQs over 80) for the validity studies. Adequate IR and TRR occurred for task ratings and general codings. General ratings provided clearer discrimination between groups and showed higher TRR than did task codings. General ratings differed both for autistic-nonautistic comparisons and for comparisons of autistic Ss of different intellectual levels. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Lord, C., S. Storoschuk, et al. (1993). "Using the ADI-R to diagnose autism in preschool children." *Infant Mental Health Journal*, 14(3), 234-252.

Describes the use of the Autism Diagnostic Interview--Revised (ADI--R) in the diagnosis of 51 autistic (AT) and 43 nonautistic (NAT) mentally handicapped preschool children of equivalent mental and chronological age. Significant differences occurred between the groups on every diagnostic subdomain from the Mental Disorders-IV (DSM-IV)/International Classification of Diseases (ICD-10) draft criteria, except specific aspects of stereotyped language. All but one of the 51 children judged to be AT by clinical observation and only 2 of the 30 NAT mentally handicapped children with mental ages of 18 mo or higher met criteria for autism on an algorithm to DSM-IV/ICD-10 draft criteria. Discrimination using domain totals between AT and the 13 NAT, nonverbal mentally handicapped children with mental ages under 18 mo was poor. Quality of social overtures to adults and peers, play, and unusual sensory behaviors and mannerisms continued to differentiate these 2 groups. (French, Spanish & Japanese abstracts) (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Mahr, R. N., P. J. Moberg, et al. (1996). "Neuropsychiatry of 18q- syndrome." *American Journal of Medical Genetics*, 67(2), 172-8.

Our understanding of neuropsychiatric abnormalities in patients with deletions of the long arm of chromosome 18 (18q- syndrome) is based mainly on sporadic case reports. We characterized the neuropsychiatric phenotype in 27 patients across a wide age range (2-47 years) with breakpoints ranging from 18q22.3-18q21.2. Adaptive behavior scores (Vineland Composite) were significantly higher in females than in males (62 +/- 5 vs. 43 +/- 3). Intelligence ranged from borderline to severely deficient (IQ, 73- < 40), with academic achievement similarly impaired. Performance in specific neuropsychological functions, including attention, novel problem solving, memory, language, visuomotor integration, and fine motor dexterity, was consistently in the moderately-to-severely impaired range. Behavioral problems were common in both sexes, including aggressivity, hyperactivity, and temper tantrums. Contrary to the few previous reports, we found no evidence of psychosis in any patients. In a subset of patients selected on the basis of no prior knowledge of behavioral problems, 1 of 16 patients (6%) had autism, as defined by the Autistic Diagnostic Interview--Revised (ADI-R) [Lord et al., 1994: *J Autism Dev Disord* 24:659-685]. Thus, the prevalence of autism in 18q- syndrome is probably no greater than that in other developmental disabilities with a similar level of cognitive impairment. In contrast to what has been believed since 18q- was first described 30 years ago, we found no relationship between chromosome deletion size and any measure of cognition or behavior; nor were there any correlations between any of these measures with the presence or absence of abnormalities on MRI or somatosensory-evoked potentials.

McLennan, J. D., C. Lord, et al. (1993). "Sex differences in higher functioning people with autism." *Journal of Autism and Developmental Disorders*, 23(2), 217-227.

Though a sex difference in the incidence of autism has frequently been reported, few studies have considered sex differences in the severity of features associated with autism. The Autism Diagnostic Interview (ADI) was used to assess the difference between a group of 21 females and 21 males with autism with equivalent chronological nonverbal IQ greater than 60. Males were rated to be more severely autistic than females on several measures of early social development, but not in any other areas. Results are discussed in relationship to hypotheses based on sex differences in other populations.

Poustka, F. and S. Lisch (1993). "Autistic behaviour domains and their relation to self-injurious behaviour." *Acta Paedopsychiatrica: International Journal of Child & Adolescent Psychiatry*, 56(2), 69-73.

Examined whether or not self-injury was associated with autistic phenomena or with degree of intellectual retardation in 69 patients (aged 5-33 yrs old) with autism assessed according to criteria of the Autism Diagnostic Interview. Intelligence was assessed with the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for Children (WISC). Findings show an association between low IQ and more frequent and severe self-injuries in the total S population and a high prevalence of self-injurious behavior among 4-5 yr old Ss. However, there were no correlations between self-injury and the different areas of autistic behavior, including communication impairment, reciprocal social interaction, and repetitive behaviors, or between self-injury

and particular symptoms such as anxiety, social disinhibition, or hyperactivity.
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Poustka, F., S. Lisch, et al. (1996). "The standardized diagnosis of autism, Autism Diagnostic Interview-Revised: Interrater reliability of the German form of the interview." *Psychopathology*, 29(3), 145-153.

The feasibility and reliability of the German form of the revised parental interview to diagnose autism (Autism Diagnostic Interview-Revised, ADI-R) was investigated in this study. Brief examples of the description of formerly and currently used diagnostic guidelines are given as well as an outline of the interview algorithm which establishes thresholds for inclusion criteria. An excellent-to-good reliability could be demonstrated for the main symptoms according to the classification rules of the ICD-10 and DSM-IV for a sample of autistic subjects at different ages and intellectual levels. The results approve the use of this interview for research and clinical purposes.
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Ruhl, D., K. Werner, et al. (1995). "[The intelligence structure of autistic persons]." *Zeitschrift für Kinder- und Jugendpsychiatrie*, 23(2), 95-103.

In a research project on the genetics of autistic disorders 115 subjects were examined. An autistic disorder was diagnosed in 102 of the subjects using the standardized Autism Diagnostic Interview (ADI; Le Couteur et al., 1989/ADI-R; Lord et al., 1994). The WAIS-R or WISC-R could be administered to 42 of the subjects. The mean full-scale IQ was 84.4, slightly below the range of normal intelligence. The mean verbal IQ (89.3) was considerably higher than the performance IQ (78.9). Analysis of the subtest patterns showed the highest scores to be in those subtests measuring knowledge of dates and facts and visuospatial abilities. The lowest scores were on subtests requiring an understanding of social relations and the ability to understand concrete social actions. This subtest pattern confirms results of other studies on the intelligence of individuals with autism and was independent of gender and level of intelligence. The subtest pattern appears to be specific for autistic disorder; it has been interpreted with reference to the theory of "weak central coherence" (Frith, 1989; Shah & Frith, 1993), which postulates that in autistic individuals stimulus perception and processing occurs independently of the general context. The results suggest that the differentiation between different types of autistic disorders should be abandoned in favor of a continuum of autistic disorders with differing degrees of severity.

Smalley, S. L., P. E. Tanguay, et al. (1992). "Autism and tuberous sclerosis." *Journal of Autism & Developmental Disorders*, 22(3), 339-355.

Tuberous sclerosis complex (TSC) is a genetic disorder with behavioral manifestations including autism. A literature review of the 2 disorders substantiates a significant association of autism and TSC. Initial data collected on 13 TSC probands (mean age 10.1 yrs) and 14 autistic probands (mean age 8.9 yrs) in a family study identified 7 TSC Ss with autism. The 7 TSC autistic Ss were similar to non-TSC autistic Ss on the social and communication domains of the Autism Diagnostic Inventory of A. LeCouteur et al (see record 1990-00113-001), but showed fewer repetitive rituals. There were more male than female TSC Ss with autism, despite an equal sex ratio among TSC

Ss. The TSC probands S with autism had significantly more seizures and mental retardation than did TSC Ss. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Spiker, D., L. Lotspeich, et al. (1994). "Genetics of Autism - Characteristics of Affected and Unaffected Children from 37 Multiplex Families." *American Journal of Medical Genetics*, 54(1), 27-35.

Evidence from twin and family studies strongly suggests that genetic factors play a prominent role in the etiology of some cases of infantile autism. Genetic factors would be expected to be especially strong in families with multiple autistic members (multiplex families). This report describes the identification and evaluation of 44 families with two or more autistic children collected as part of a genetic linkage study in autism. Families were referred with a presumptive classification of multiplex autism. Children referred as autistic, as well as their presumptively normal siblings, were assessed using the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Scale (ADOS). Thirty-seven of the 44 families (87%) had at least two children who met diagnostic criteria for autism on the ADI. Of the total group of 117 children evaluated in those families, 83 (71%) met all ADI criteria and could be unambiguously classified as autistic (affected), 26 (22%) met none of the ADI criteria and were classified as not autistic (unaffected), and 8 (7%) were classified as uncertain because they met one or more but not all of the ADI cutpoints. Autistic siblings were not significantly concordant for most autism characteristics, for IQ, or for verbal ability. Significant concordances were found, however, for behaviors related to rituals and repetitive play, and for social impairments in the expression and understanding of facial expressions of emotion. The results of this study suggests two major points: first, there does not appear to be a highly variable autistic phenotype expressed in multiplex families; in the vast majority of cases, children are either clearly affected or clearly unaffected, so that linkage analysis should not be complicated by a large number of ambiguous or uncertain cases. Second, multiplex families do not appear to associate into subgroups defined by clustering of specific autism behaviors. (C) 1994 Wiley-Liss, Inc.

Szatmari, P., L. Archer, et al. (1995). "Asperger's syndrome and autism: Differences in behavior, cognition, and adaptive functioning." *Journal of the American Academy of Child & Adolescent Psychiatry*, 34(12), 1662-1671.

Examined differences in behavior, cognition, and adaptive functioning in 47 children with autism and 21 with Asperger's syndrome (all Ss aged 4-6 yrs), differentiated from pervasive developmental disorder (PDD) on the basis of delayed and deviant language development. Ss completed the Autism Diagnostic Interview, Vineland Adaptive Behavior Scales, Leiter International Performance Scale, Stanford Binet Intelligence Scale, Reynell Developmental Language Scales, and the Beery Developmental Test of Visual-Motor Integration. Significant differences between the groups existed on many PDD symptoms, adaptive behaviors, and cognitive measures of language competence, but not on aspects of nonverbal communication, nonverbal cognition, or motor development. Results indicate that subtypes of children with PDD can be identified that differ on variables relatively independent of defining characteristics. (PsycINFO Database Record (c) 2000 APA, all rights reserved)

Yirmiya, N., M. Sigman, et al. (1994). "Comparison between Diagnostic Instruments for Identifying High-Functioning Children with Autism." *Journal of Autism and Developmental Disorders*, 24(3), 281-291.

Two instruments for identifying autism in children and adolescents with intellectual abilities in the normal range were compared. Diagnostic tools consisted of the Autism Behavior Checklist (ABC) and the Autism Diagnostic Interview (ADI). The sample was composed of 18 children who were all diagnosed as having either infantile autism or infantile autism, residual state based on DSM-III criteria by a clinical team using observations, parental interviews, and interactions with the children. Only 4 of the children met diagnostic cutoffs for autism on the current ABC but all met criteria for diagnosis on the ABC using parental recall of the child's behavior at 3-5 years of age. The ADI had somewhat greater specificity in that 3 children did not meet criteria for diagnosis although 2 of these children also received ABC scores based on parental recollection that were in the borderline range.