

Recent Publications from the Utah Autism Research Program and the Collaborative Programs of Excellence in Autism (4/2005)

Bigler ED, Tate DF, Neeley ES, Wolfson LJ, Miller MJ, Rice SA, Cleavenger H, Anderson C, Coon H, Ozonoff S, Johnson M, Dinh E, Lu J, McMahon W, Lainhart JE.

Temporal lobe, autism and macrocephaly. *American Journal of Neuroradiology*, 2003 Nov-Dec; 24 (10) 2066-76.

Abstract: *Background and Purpose:* Because of increased prevalence of macrocephaly in autism, head size must be controlled for in studies that examine volumetric findings of the temporal lobe in autistic subjects. We prospectively examined temporal lobe structures in individuals with autism who were normocephalic or macrocephalic (head circumference > 97th percentile) and in control subjects who were normocephalic or macrocephalic or who had a reading disorder (unselected for head size). The rationale for the reading disorder group was to have control subjects with potential temporal lobe anomalies, but who were not autistic. *Methods:* In individuals aged 7-31 years, autism was diagnosed on the basis of standardized interview and diagnostic criteria. Control subjects ranged in age from 7 to 22 years. All subjects were male. MR morphometrics of the major temporal lobe structures were based on ANALYZE segmentation routines, in which total brain volume and total intracranial volume (TICV) were calculated. Both group comparisons and developmental analyses were performed. *Results:* No distinct temporal lobe abnormalities of volume were observed once head size (TICV) was controlled for. In autistic and control subjects, robust growth patterns were observed in white and gray matter that differed little between the groups. Although subtle differences were observed in some structures (i.e., less white matter volume in the region of the temporal stem and overall temporal lobe), none was statistically significant. *Conclusion:* No major volumetric anomalies of the temporal lobe were found in cases of autism when IQ, TICV, and age were controlled. Temporal lobe abnormalities that may be associated with autism are likely to be more related to functional organization within the temporal lobe than to any gross volumetric difference.

Coon H, Dunn D, Lainhart J, Miller J, Hamil C, Battaglia A, Tancredi R, Leppert MF, Weiss R, McMahon W.

Possible association between autism and variants in the brain-expressed tryptophan hydroxylase gene (TPH2).

Am J Med Genet B Neuropsychiatr Genet. 2005 Mar 14; [Epub ahead of print]

Abstract: We report a possible association between autism in our sample and a recently described brain-expressed tryptophan hydroxylase gene (TPH2). The well-replicated involvement of the serotonin neurotransmitter system in autism has stimulated interest in many genes in the serotonin pathway as possible candidates for mutations leading to autism susceptibility. Serotonin synthesis is controlled by the rate-limiting enzyme tryptophan hydroxylase. A mouse study of the original tryptophan hydroxylase gene (TPH1) and the new isoform (TPH2) showed that while TPH1 is primarily expressed peripherally, TPH2 is found exclusively in brain tissue. We searched for human sequence variants in 6,467 nucleotides covering all 11 exons of TPH2, and also 248 nucleotides upstream of the start codon, and 935 nucleotides downstream of the stop codon. Eighteen variants were characterized in 88 subjects with autism studied at our two centers, and 95 unrelated control subjects. Using a model-free association method and empirical P value estimation, two variants showed frequency differences between autism and control subjects ($P = 0.01$ for a T-G variant in intron 1, and $P = 0.02$ for a A-T variant in intron 4). A haplotype including these variants showed slightly increased significance ($P = 0.005$). Further investigation of clinical phenotypes showed a possible association between presence of the variants at these two SNPs and higher scores on the Autism Diagnostic Interview (ADI) domain describing repetitive and stereotyped behaviors ($P = 0.007$). We conclude that TPH2 may play a modest role in autism susceptibility, perhaps relating specifically to repetitive behaviors, pending replication of this result.

Devlin B, Bennett P, Cook EH Jr, Dawson G, Gonen D, Grigorenko EL, McMahon W, Pauls D, Smith M, Spence MA, Schellenberg GD.

No evidence for linkage of liability to autism to HOXA1 in a sample from the CPEA network. *Am J Med Genet.* (2002). 114(6):667-72.

Abstract: A recent study by Ingram et al. [2000b: *Teratology* 62:393-405] suggests a His73^{Arg} polymorphism (A:G) in *HOXA1* contributes substantially to a liability for autism. Using 68 individuals diagnosed with Autism Spectrum Disorders, they found a significant dearth of G homozygotes and biased transmission of G alleles from parents to affected offspring, especially from mothers. Because the connection between *HOXA1* and liability to autism is compelling, we attempted to replicate their finding using a larger, independent sample from the Collaborative Programs of Excellence in Autism (CPEA) network. In our data, genotype frequencies conform to Hardy-Weinberg equilibrium; allele transmissions meet Mendelian expectations; and there is no obvious sex-biased allele transmission. Based on our sample size, calculations suggest that we would have at least 95% power to detect linkage and association even if the A:G polymorphism were to account for only 1% of the heritability of autism. Therefore, although we cannot exclude the possibility that the samples in the two studies are intrinsically different, our data from our sample argue against a major role for *HOXA1* His73^{Arg} in liability to autism.

Devlin B, Bennett P, Dawson G, Figlewicz DA, Grigorenko EL, McMahon W, Minshew N, Pauls D, Smith M, Spence MA, Rodier PM, Stodgell C, Schellenberg GD; CPEA Genetics Network.

Alleles of a reelin CGG repeat do not convey liability to autism in a sample from the CPEA network. *Am J Med Genet B Neuropsychiatr Genet.* 2004 Apr 1;126(1):46-50.

Abstract: 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.

Gale S, Ozonoff S, Lainhart J.

Brief report: pitocin induction in autistic and nonautistic individuals. *J Autism Dev Disord.* 2003 Apr;33(2):205-8.

Abstract: Oxytocin plays an important role in social-affiliative behaviors. It has been proposed that exposure to high levels of exogenous oxytocin at birth, via pitocin induction of delivery, might increase susceptibility to autism by causing a downregulation of oxytocin receptors in the developing brain. This study examined the rates of labor induction using pitocin in children with autism and matched controls with either typical development or mental retardation. Birth histories of 41 boys meeting the criteria for autistic disorder were compared to 25 age- and IQ-matched boys without autism (15 typically developing and 10 with mental retardation). There were no differences in pitocin induction rates as a function of either diagnostic group (autism vs. control) or IQ level (average vs. subaverage range), failing to support an association between exogenous exposure to oxytocin and neurodevelopmental abnormalities.

Hasan KM, Alexander AL, Narayana PA.

Does fractional anisotropy have better noise immunity characteristics than relative anisotropy in diffusion tensor MRI? An analytical approach. *Magn Reson Med.* 2004 Feb;51(2):413-7.

Abstract: Fractional anisotropy (FA) and relative anisotropy (RA) are the two most commonly used scalar measures of anisotropy in diffusion tensor (DT) MRI. While a few published studies have shown that FA has superior noise immunity relative to RA, no theoretical basis has been proposed to explain this behavior. In the current study, the diffusion tensor invariants were used to derive a simple analytical expression that directly relates RA and FA. An analysis based on that analytical expression demonstrated that the FA images have a higher signal-to-noise ratio (SNR) than RA for any value of tensor anisotropy RA or FA > 0. This theoretical behavior was verified using both Monte Carlo simulations and bootstrap analysis of DT-MRI data acquired in a spherical water phantom and normal human subjects.

Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL.

Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns.

Am J Neuroradiol. 2004 Mar;25(3):356-69.

King BH, Wright DM, Handen BL, Sikich L, Zimmerman AW, McMahon W, Cantwell E, Davanzo PA, Dourish CT, Dykens EM, Hooper SR, Jaselskis CA, Leventhal BL, Levitt J, Lord C, Lubetsky MJ, Myers SM, Ozonoff S, Shah BG, Snape M, Shernoff EW, Williamson K, Cook EH Jr.

Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *J Am Acad Child Adolesc Psychiatry.* (2001). 40(6):658-65.

Abstract: *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.

Krasny L, Williams BJ, Provencal S, Ozonoff S.

Social skills intervention for the autism spectrum: Essential ingredients and a model curriculum. *Child Adolesc Psychiatric Clin N Am,* (2003). 12: 107-122.

Abstract: Despite widespread recognition that social deficits are core features of autism spectrum disorders, few treatment programs for improving social adaptation have been developed. Curricula designed to practice social skills in a group setting are vital, but few are yet commercially available. This article outlines several elements the authors believe are important to successful group social skills intervention. Specific examples translating these principles into actual practice are provided. Illustrations from social skills groups conducted at the University of Utah are included.

Lainhart JE

Increased rate of head growth during infancy in autism.

American Journal of the American Medical Association, 2003 Jul 16; 290(3): 337-44. (Editorial)

Lainhart JE

Psychiatric problems in autistic individuals and their parents and siblings. *International Review of Psychiatry* (1999). 11: 278-298.

Abstract: The objective of this paper is to review psychiatric problems in children and adults with autism and related disorders and their first-degree relatives, with a focus on: (1) why they present with psychiatric problems; (2) rates of psychiatric disorders; (3) clinical features important in diagnosis and differential diagnosis; (4) treatment. The data come from published reports of psychiatric problems in individuals with autism, Asperger's disorder, or Pervasive Developmental Disorder Not Otherwise Specified and their relatives and the clinical experience of the author and other experts. Children and adults with autism may present with psychiatric problems because of the core defining features of autism, cognitive impairments, medical disorders, other psychiatric symptoms and disorders, and life experiences related to having autism. The data suggest that depression, anxiety, impairing compulsive behaviours, attentional problems, hyperactivity, and sleep problems occur commonly in individuals with autism. Tics and Tourette's disorder appears to occur in a substantial minority. Schizophrenia occurs infrequently. Clinical features of autism and the inapplicability of subjective diagnostic criteria make the diagnosis of other psychiatric disorders difficult in many autistic individuals. Rates of major depression and social phobia are increased in first-degree relatives of autistic probands. The burden of raising an autistic child may also contribute to the development of psychiatric problems in parents and siblings. Future studies need to determine if the risk of developing particular psychiatric disorders and problems is truly increased in individuals with autism and related disorders above the risk in the general population and in individuals with other developmental disorders. If risk is increased, potential risk factors of a genetic, neurologic, cognitive, and environmental nature will need to be identified and understood. In order to measure risk and identify risk factors, reliable, valid methods for diagnosing psychiatric disorders and problems in autistic children and adults must be developed.

Lainhart JE, Ozonoff S, Coon H, Krasny L, Dinh E, Nice J, McMahon W

Autism, regression, and the broader autism phenotype. *Am J Medical Genetics*, (2002). 113(3):231-237.

Abstract: The broader autism phenotype (BAP) is a subclinical set of personality and other features that is thought to index familiarity and/or genetic liability to autism. Eighteen parents of autistic probands with a history of language regression and 70 parents of autistic probands without regression were assessed for features of the BAP and compared with published rates in parents of nonautistic subjects. Parents of probands with regressive and nonregressive autism demonstrated similar rates of the BAP (27.8% vs. 32.9%; $P = 0.33$). The rate of the BAP was significantly higher in both groups of autism parents than in parents of nonautistic subjects ($P \leq 0.01$). Thus, this measure of genetic liability is increased equally in families with both forms of autism when compared with controls. Environmental events are therefore unlikely to be the sole cause of regressive autism in our sample. Environmental events, however, may act in an additive or "second-hit" fashion in individuals with a genetic vulnerability to autism.

Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, Folstein SE.

Macrocephaly in children and adults with autism. *J Am Acad Child Adolesc Psychiatry*. (1997). 36(2):282-90.

Abstract: OBJECTIVE: To explore the frequency and onset of macrocephaly in autism and its relationship to clinical features. METHOD: Head circumferences at birth, during early childhood, and at the time of examination were studied in a community-based sample of autistic children and adults. The authors investigated whether head circumference at the time of examination was associated with clinical features. RESULTS: Fourteen percent of the autistic subjects had macrocephaly: 11% of males and 24% of females. In most, the macrocephaly was not present at birth; in some it became apparent in early and middle childhood as a result of increased rate of head growth. A small relationship was noted between head circumference percentile and less severe core features of autism. Neither macrocephaly nor head circumference percentile was associated with nonverbal IQ, verbal status, seizure disorder, neurological soft signs or minor physical anomalies in the autistic subjects. CONCLUSION: Macrocephaly is common in autism and usually is not present at birth. Rates of head growth may be abnormal in early and middle childhood in some (37%) children with autism. Macrocephaly does not define a homogeneous subgroup of autistic individuals according to clinical features.

Lajiness-O'Neill R, Beaulieu I, Titus J, Asamoah A, Bigler E, Bawle E, Pollack R.

Memory and Learning in Children with 22q11.2 Deletion Syndrome: Evidence for Ventral and Dorsal Stream Disruption? *Neuropsychol Dev Cogn C Child Neuropsychol*. 2005;11(1):55-71.

Abstract: This study examined memory functioning in children and adolescents with 22q11.2 Deletion Syndrome (DS; velocardiofacial syndrome). An overall verbal better than nonverbal memory pattern was evident on the Test of Memory and Learning (TOMAL), with children with 22q11.2 DS performing significantly below their siblings and children with low average IQ but similar to children with autism on facial memory. Children with 22q11 DS also performed significantly below their siblings on tests of verbal working memory. Children with autism performed significantly poorer than the siblings of children with 22q11.2 DS only on their recall of stories. Delayed recall was significantly poorer in children with 22q11.2 DS and children with autism, compared to sibling controls. Although there were no significant group differences on tests of multiple trial verbal or visual learning, a relative weakness was noted with multiple trial visual learning in children with 22q11.2 DS and their siblings, suggesting that an alternative or interactive factor other than the deletion may account for the relatively better verbal compared to nonverbal memory abilities. Deficits in facial memory in children with both 22q11.2 DS and autism suggest disruptions in ventral temporal pathways such as between fusiform gyrus and parahippocampal/hippocampal regions whereas deficits in verbal working memory in children with 22q11.2 DS implicates dorsolateral prefrontal regions, both intimating aberrant white matter pathways.

Lazar M, Alexander AL.

Bootstrap white matter tractography (BOOT-TRAC). *Neuroimage*. 2005 Jan 15;24(2):524-32. Epub 2004 Nov 24.

Abstract: White matter tractography is a noninvasive method for estimating and visualizing the white matter connectivity patterns in the human brain using diffusion tensor imaging (DTI) data. Sources of experimental noise may induce errors in the measured fiber directions, which will reduce the accuracy of the estimated white matter trajectories. In this study, a statistical nonparametric bootstrap method is described for estimating the dispersion and other errors in white matter tractography results. Prior studies have derived models of tractography error using the signal-to-noise ratio (SNR) and diffusion anisotropy of the DTI data. Tractography errors measured using bootstrap methods were generally consistent with an analytic model of tractography error except in areas where branching was evident. White matter tractography with bootstrap resampling is also applied to estimate the probabilities of connection between brain regions. The approach was used to generate probabilistic connectivity maps between the cerebral peduncles and specific cortical regions.

Lazar M, Alexander AL.

An error analysis of white matter tractography methods: synthetic diffusion tensor field simulations. *Neuroimage*. 2003 Oct;20(2):1140-53.

Abstract: White matter tractography using diffusion tensor MR images is a promising method for estimating the pathways of white matter tracts in the human brain. The success of this method ultimately depends upon the accuracy of the white matter tractography algorithms. In this study, a Monte Carlo simulation was used to investigate the impact of SNR, tensor anisotropy, and diffusion tensor encoding directions on the accuracy of six tractography algorithms. The accuracy was assessed in straight and curved tracts and tract geometries with divergence properties. In general, the tract dispersion increased with distance and decreased with SNR and anisotropy. The tract orientation with respect to the encoding scheme also influenced tract dispersion. Divergent tract geometries increased tract dispersion, whereas convergent tract geometries reduced dispersion. Analytic models of tract dispersion were constructed as a function of the tract distance, SNR, eigenvalues of the tracts, voxel size, and the relationship between the tract direction and the diffusion tensor encoding directions. In certain cases, the mean tract trajectory was found to deviate from the ideal pathway for curved trajectories. Analytical models of mean displacement were constructed as a function of the curvature, tract distance, step size, and tensor eigenvalues. These models may be used in future studies to assess the level of confidence associated with a tractography result.

Lazar M, Weinstein DM, Tsuruda JS, Hasan KM, Arfanakis K, Meyerand ME, Badie B, Rowley HA, Houghton V, Field A, Alexander AL.

White matter tractography using diffusion tensor deflection. *Hum Brain Mapp*. 2003 Apr;18(4):306-21.

Abstract: Diffusion tensor MRI provides unique directional diffusion information that can be used to estimate the patterns of white matter connectivity in the human brain. In this study, the behavior of an algorithm for white matter tractography is examined. The algorithm, called TEND, uses the entire diffusion tensor to deflect the estimated fiber trajectory. Simulations and imaging experiments on in vivo human brains were performed to investigate the behavior of the tractography algorithm. The simulations show that the deflection term is less sensitive than the major eigenvector to image noise. In the human brain imaging experiments, estimated tracts were generated in corpus callosum, corticospinal tract, internal capsule, corona radiata, superior longitudinal fasciculus, inferior longitudinal fasciculus, fronto-occipital fasciculus, and uncinate fasciculus. This approach is promising for mapping the organizational patterns of white matter in the human brain as well as mapping the relationship between major fiber trajectories and the location and extent of brain lesions.

Libbey J, Sweeten T, McMahon W, Fujinami R.

Autistic disorder and viral infections. *J Neurovirol*. 2005 Feb;11(1):1-10.

Abstract: Autistic disorder (autism) is a behaviorally defined developmental disorder with a wide range of behaviors. Although the etiology of autism is unknown, data suggest that autism results from multiple etiologies with both genetic and environmental contributions, which may explain the spectrum of behaviors seen in this disorder. One proposed etiology for autism is viral infection very early in development. The mechanism, by which viral infection may lead to autism, be it through direct infection of the central nervous system (CNS), through infection elsewhere in the body acting as a trigger for disease in the CNS, through alteration of the immune response of the mother or offspring, or through a combination of these, is not yet known. Animal models in which early viral infection results in behavioral changes later in life include the influenza virus model in pregnant mice and the Borna disease virus model in newborn Lewis rats. Many studies over the years have presented evidence both for and against the association of autism with various viral infections. The best association to date has been made between congenital rubella and autism; however, members of the herpes virus family may also have a role in autism. Recently, controversy has arisen as to the involvement of measles virus and/or the measles, mumps, rubella (MMR) vaccine in the development of autism. Biological assays lend support to the association between measles virus or MMR and autism whereas epidemiologic studies show no association between MMR and autism. Further research is needed to clarify both the mechanisms whereby viral infection early in development may lead to autism and the possible involvement of the MMR vaccine in the development of autism.

Owley T, McMahon, W, Cook EH, Lahlere T, South M, Mays LZ, Shernoff ES, Lainhart J, Modahl CB, Corsello C, Ozonoff S, Risi S, Lord C, Leventhal BL, Filipek, PA.

Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. *J Am Acad Child Adolesc Psychiatry.* (2001). 40(11):1293-9.

Abstract: *Objective:* To examine the efficacy of intravenous porcine secretin for the treatment of autistic disorder. *Method:* Randomized, double-blind, placebo-controlled, crossover design. Fifty-six subjects with autistic disorder received either a secretin or placebo infusion at baseline and the other substance at week 4. Subjects were given the Autism Diagnostic Observation Schedule (ADOS) and other pertinent developmental measures at baseline and at weeks 4 and 8 to assess drug effects. *Results:* For the primary efficacy analysis, change of ADOS social-communication total score from week 0 to week 4, no statistically significant difference was obtained between placebo (-0.8 ± 2.9) and secretin groups (-0.6 ± 1.4 ; $t_{54} = 0.346$, $p < .73$). The other measures showed no treatment effect for secretin compared with placebo. *Conclusion:* There was no evidence for efficacy of secretin in this randomized, placebo-controlled, double-blind trial.

Ozonoff S, Cook I, Coon H, Dawson G, Joseph RM, Klin A, McMahon WM, Minshew N, Munson JA, Pennington BF, Rogers SJ, Spence MA, Tager-Flusberg H, Volkmar FR, Wrathall D.

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. *J Autism Dev Disord.* 2004 Apr;34(2):139-50.

Abstract: 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.

Ozonoff S, Garcia N, Clark E, Lainhart JE.

MMPI-2 personality profiles of high-functioning adults with autism spectrum disorders. *Assessment.* 2005 Mar;12(1):86-95.

Abstract: The Minnesota Multiphasic Personality Inventory-Second Edition was administered to 20 adults with autism spectrum disorders (ASD) who fell in the average to above average range of intelligence and 24 age-, intelligence-, and gender-matched college students. Large group differences, with the ASD group scoring higher, were found on the L validity scale, Clinical Scales 2 (D) and 0 (Si), Content scale Social Discomfort (SOD), Supplementary scale Repression (R), and Personality Psychopathology Five (PSY-5) scale INTR (Introversion). The proportion of ASD adults scoring in the clinical range on these scales was between 25% and 35%. High scores on these scales are consistent with the clinical picture of Asperger syndrome and high-functioning autism in adulthood. Future directions and implications for identifying adults in need of a specialized autism assessment are discussed.

Rice SA, Bigler ED, Cleavinger HB, Tate DF, Sayer J, McMahon W, Ozonoff S, Lu J, Lainhart JE.

Macrocephaly, corpus callosum morphology, and autism. *J Child Neurol.* 2005 Jan;20(1):34-41.

Abstract: 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.

South M, Williams BJ, McMahon W, Owley T, Filipek PA, Shernoff E, Corsello C, Lainhart J, Landa R, Ozonoff S.

Utility of the Gilliam Autism Rating Scales in research and clinical populations *Journal of Autism and Developmental Disorders*, (2002), 32, 593-599.

Abstract: The Gilliam Autism Rating Scale (GARS; Gilliam, 1995) was developed as a relatively easy, inexpensive aid in the surveillance and diagnosis of autism. This study examined the validity of the GARS when used with a sample of 119 children with strict DSM-IV diagnoses of autism, ascertained from both clinical and research settings. The GARS consistently underestimated the likelihood that autistic children in this sample would be classified as having autism. The sample mean for the Autism Quotient, a hypothesized index of the likelihood of having autism, was 90.10, significantly below the reference mean of 100. Diagnostic classification according to criteria specified by the GARS resulted in a sensitivity of only .48. Limitations of rating scales in general and of the GARS specifically are discussed. It is recommended that clinicians and researchers using or considering using the GARS for autism diagnosis or ratings of autism severity recognize the need for further research regarding its use.

Wilde EA, Hunter JV, Newsome MR, Scheibel RS, Bigler ED, Johnson JL, Fearing MA, Cleavinger HB, Li X, Swank PR, Pedroza C, Roberson GS, Bachevalier J, Levin HS.

Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. *Journal of Neurotrauma.* 2005 Mar;22(3):333-44.

Abstract: In vivo MRI volumetric analysis enables investigators to evaluate the extent of tissue loss following traumatic brain injury (TBI). However, volumetric studies of pediatric TBI are sparse, and there have been no volumetric studies to date in children examining specific subregions of the prefrontal and temporal lobes. In this study, MRI volumetry was used to evaluate brain volume differences in the whole brain, and prefrontal, temporal, and posterior regions of children following moderate to severe TBI as compared to uninjured children of similar age and demographic characteristics. The TBI group had significantly reduced whole brain, and prefrontal and temporal regional tissue volumes as well as increased cerebrospinal fluid (CSF). Confidence interval testing further revealed group differences on gray matter (GM) and white matter (WM) in the superior medial and ventromedial prefrontal regions, WM in the lateral frontal region, and GM, WM, and CSF in the temporal region. Whole brain volume and total brain GM were reduced, and total ventricular volume, total CSF volume, and ventricle-to-brain ratio (VBR) were increased in the TBI group. Additional analyses comparing volumetric data from typically developing children and subgroups of TBI patients with and without regional focal lesions suggested that GM loss in the frontal areas was primarily attributable to focal injury, while WM loss in the frontal and temporal lobes was related to both diffuse and focal injury. Finally, volumetric measures of preserved frontotemporal tissue were related to functional recovery as measured by the Glasgow Outcome Scale (adapted for children) with greater tissue preservation predicting better recovery.

Yu CE, Dawson G, Munson J, D'Souza I, Osterling J, Estes A, Leutenegger AL, Flodman P, Smith M, Raskind WH, Spence MA, McMahon W, Wijsman EM, Schellenberg GD.

Presence of large deletions in kindreds with autism. *Am J Hum Genet.* (2002). 71(1):100-15.

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