

# A SYSTEMS NEUROSCIENCE APPROACH TO AUTISM: BIOLOGICAL, COGNITIVE, AND CLINICAL PERSPECTIVES

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Autism is a behaviorally defined disorder characterized by a broad constellation of symptoms. Numerous studies directed to the biological substrate demonstrate clear effects of neurodevelopmental differences that will likely point to the etiology, course, and long-term outcomes of the disorder. Consistently replicated research on the neural underpinnings of autism is reviewed. In general, results suggest several main conclusions: First, autism is a heterogeneous disorder and is likely to have multiple possible etiologies; second, structural brain studies have indicated a variety of diffuse anatomical differences, reflective of an early developmental change in the growth or pruning of neural tissue, rather than localized lesions; similarly, neurochemical studies suggest early, neuromodulatory discrepancies rather than gross or localized abnormalities; and finally, there are a number of limitations on studies of brain activity that to date preclude definitive answers to questions of how the brain functions differently in autism. The large number of active research programs investigating the cognitive neuroscience of autism spectrum disorders, in combination with the exciting development of new methodologies and tools in this area, indicates the drama and excitement of work in this area.

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Autism is a neurodevelopmental disability characterized by severe and persistent deficits in three primary areas of functioning: impairments in social reciprocity and engagement; language and communicative skills; and the presence of repetitive nonfunctional behaviors and stereotyped interests [American Psychiatric Association, 1994]. The study of a disorder such as autism sheds light on the disorder itself, but also improves our understanding of normal development and functioning [Cicchetti and Rogosch, 1996]. This review summarizes some of the methodological approaches to studying autism, drawing on background from other contributions to this special issue. One overarching theme is the challenge of understanding the biological basis of a disorder, diagnosed only through behavioral criteria, with a heterogeneous set of symptoms that cross multiple domains [McBride et al., 1996].

“Autism spectrum disorders” (ASD) are viewed as a set of disorders that span a wide spectrum of functioning [Folstein and Rosen-Scheidley, 2001]. Included in the definition of Pervasive Developmental Disorders are classic autism, Asperger syndrome,

Rett syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD/NOS). All the disorders are characterized by early-arising deficits in the social and communicative domains, although Rett syndrome and Disintegrative Disorder encompass a period of apparently typical growth and development followed by a significant loss of skills [see Lord and Risi, 2000, for an overview]. Similarly, one third of the parents of children with autism report a normal early developmental trajectory, with subsequent loss of function.

The *spectrum* of autism refers both to the relatively heterogeneous disorders that make up the autism “family” of diagnoses, and to the wide variety in functional abilities. While approximately 75% of individuals with autism experience comorbid mental retardation (MR), sometimes in the severe or profound range, the remaining 25% have intellectual abilities that range from low average to above average. Similarly, while many individuals may require supervision and sheltered living arrangements later in life, others may not only live independently, but also may start families and coordinate independent careers (although the latter cohort is less frequent). Researchers have suggested that increased recognition of the higher-functioning end of the spectrum is what accounts, in part, for the increase in ASD diagnoses over the past decade [Fombonne, 1999].

The autism spectrum has been expanded even further by the notion of the Broader Autism Phenotype, encompassing milder autism-like impairments in both psychological and biological functioning [Fombonne et al., 1997; Pickles et al., 2000]. As early as 1957, clinical and experimental studies have demonstrated sub-clinical autistic symptomatology in family members of affected individuals [Eisenberg, 1957], including executive dysfunction (see below) in parents [Hughes et al., 1997] and siblings [Hughes et al., 1999] of children with autism, and social

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impairments in parents of affected children [Wolff et al., 1988]. Parents of affected children exhibit subtle language and communicative differences [Landa et al., 1991; 1992] and experience higher rates of major depressive disorder (19%) and social phobia [15%; Piven and Palmer, 1999]. There is evidence of elevated blood serotonin levels (hyperserotonemia) in family members [Leboyer et al., 1999]. (Note that the latter is not pathognomic, and there are no clear boundaries between “elevated” and “normal” levels.)

## BEHAVIORAL AND COGNITIVE CHARACTERISTICS OF AUTISM

### Social Reciprocity

Individuals with autism exhibit delays or failures of development in three primary arenas of social reciprocity: *interpersonal relatedness*, a failure to coordinate affective perspectives with others [Hobson, 1986]; *joint attention*, the ability to coordinate one’s attention to an object with another person [McArthur and Adamson, 1996]; and *imitation*, the mimicking of facial expressions [typically seen in newborns; Meltzoff, 1988], playful imitation of others, and voluntary gestural imitation [Rogers et al., 1996]. However, social responsiveness is not simply absent; even lower-functioning children make social overtures and display communicative intent [Lord and Paul, 1997].

### Language and Communication

Although communicative deficits can range from mutism to adequate speech with poor conversational skills, as many as 50% of individuals with autism fail to develop functional spoken language abilities [Bryson et al., 1988]. The most-studied aspects of language in ASD are pragmatic and discourse processes, including conversational skills, implicit meanings, and nonverbal communication [Baron-Cohen et al., 1985; Mundy and Markus, 1997], with individuals of all ages exhibiting deficits [Bartak et al., 1975]. The unique speech style characteristic of ASD includes atypical intonation, prosody, and other speech qualities [Rutter et al., 1992]. Communicative impairments extend into the nonverbal domain, as children and adults with ASD exhibit difficulties integrating gesture and language [Lord and Pickles, 1996; Mundy et al., 1990]. While some studies have failed to demonstrate deficits in grammatical development in autism [Fein and Waterhouse, unpublished data; Howlin, 1984], others have found such

impairments [Bartolucci and Albers, 1974; Bartolucci et al., 1980; Dalgleish, 1975]. Language deficits appear to reflect deviance, rather than simple delay [Shapiro, 1977]. In general, there is a dearth of research on the psycholinguistics of young children with autism [Minshew et al., 1995].

### Repetitive Behaviors and Stereotyped Interests

Individuals with ASD typically have stereotyped behaviors and interests, including a strong resistance to changes in their environment or routines; a preoccupation with one or more fixed interests, such as train schedules or cartoon characters; a preference for repetitive object play, such as lining up cars; an insistence on ritualized actions; and stereotyped body movements involving the fingers and hands or the whole body. High-functioning individuals are equally likely to show these symptoms. While this symptom domain is the least well-studied, ritualized behaviors, stereotyped movements, and object preoccupations all seem to improve with age; however, social impairments due to circumscribed interests typically increase [South et al., unpublished data].

### Cognitive Impairments

One striking feature of ASD is the “jagged profile” of performance across subsets of IQ measures such as the Wechsler scales. Most individuals with ASD show relative strengths in tasks which demand visuospatial organization and perceptual organization abilities (such as Block Design), and relative impairments on tasks that demand planning and interpretation of practical knowledge or events [such as Picture Arrangement; Happe and Frith, 1996]. ASD is characterized by “islets of ability,” including excellent rote memory abilities, skill with jigsaw puzzles, and (in 10% of individuals with autism) savant skills such as calendrical calculation. In contrast to strong rote memory abilities, individuals with autism exhibit impairments of working memory and organizational aspects of memory [Bennetto et al., 1996; Dawson et al., 1998], although studies of children have been inconsistent [Griffith et al., 1999; Russell et al., 1996]. Children with autism often exhibit both a hyperactive style and difficulty concentrating as well as an ability to focus intently on one interest; lower-level impairments in attentional mechanisms may account for some of these findings [Townsend et al., 1996].

To account for this pattern of cognitive strengths and weaknesses, as well as the core symptoms of ASD, four prominent models have been proposed. These include (1) the Theory of Mind model [ToM; Baron-Cohen et al., 1985], in which one aspect of frontal lobe processing may be dedicated to social cognitive abilities, specifically, for understanding the psychological beliefs and feelings of others. Impairments would be secondary to the malfunctioning of this social-cognitive module; (2) the Social Orienting model [Dawson and Lewy, 1989], in which early-emerging symptoms of autism reflect core affective and social impairments, linked to dysfunction of the limbic system; (3) the Central Coherence model [Frith and Happe, 1994], characterized by impairments in the integration of information at different levels of representation, facilitating performance of tasks that require attention to local information and impairing performance of tasks that require the recognition of global meaning; and (4) the Executive Function model [Rogers and Pennington, 1991], in which behavioral impairments in ASD are secondary to deficits in frontally-mediated executive cognitive processes, including working memory.

## PREVALENCE, DIAGNOSIS AND ETIOLOGY OF AUTISM SPECTRUM DISORDERS

### Epidemiology

Recent studies indicate a prevalence for autism of 5.2 per 10,000, with 80% of affected individuals exhibiting MR; prevalence rates increase to 16–19 per 10,000 when all disorders on the spectrum are included [Fombonne, 1999]. The data do not support a secular increase in the incidence of autism; rather, recent increases in the number of individuals diagnosed with ASD are likely due to better detection and diagnosis, particularly of milder forms. It should be noted that to-date unpublished research in California may suggest a higher incidence of ASD in recent years. There is a high male to female gender ratio (4:1) in autism [Bryson, 1996].

### Co-Morbidity

Individuals with autism are at slightly higher risk for seizure disorders [lifetime prevalence of 20–35%; Rapin, 1996], especially those with MR [Rossi et al., 1995]. Individuals with Fragile X syndrome are at risk for autism [incidence of 3–25%; Bailey et al., 1993].

Individuals with tuberous sclerosis complex (TSC) are also at risk for autism (60% of individuals with TSC and MR also have autism). These individuals typically also have seizure disorders. In contrast, of all individuals with autism, under 3% have TSC [Gillberg et al., 1994]. In general, ASD is not closely associated with other neurological, psychological, or physiological disorders.

### Diagnosis and Prognosis

Across the lifespan, autism is one of the most robust diagnoses in the DSM diagnostic system, with a sensitivity of .82 and a specificity of .87 [Volkmar et al., 1994]. The accurate diagnosis of autism requires a thorough caregiver interview, an interactive assessment of the affected child, and experienced clinical judgment. Younger children (under 24 months) are the most difficult to diagnose [Volkmar and Lord, 1998]. Recently, a number of effective measures have become available. *Screening tools* include the Checklist for Autism in Toddlers [Baron-Cohen et al., 1996] and the Autism Screening Questionnaire [Berument et al., 1999]. *Parent interview instruments* include the Parent Interview for Autism [Stone and Hogan, 1993] and the Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994]. *Interactional instruments* include the Childhood Autism Rating Scale [Schopler et al., 1988] and the Autism Diagnostic Observation Schedule [ADOS; Lord et al., 1989]. The ADI-R and ADOS, which require training for reliability in administration and scoring, are the “gold standard” for diagnosis.

Many children with autism are initially referred for evaluation because of parents’ concerns about delayed language milestones [Dahlgren and Gillberg, 1989], and the attainment of these milestones appears to be strongly related to long-term prognosis [Mawhood et al., 2000]. For example, Rutter [1970] found that using language productively and flexibly by age five was the best single predictor of positive outcomes for a large sample of children with autism. Other strong predictors include the severity and the number of symptoms.

Clinicians are often reluctant to diagnose early; one report found that children in the UK were diagnosed at the age of 6 years on average [Howlin and Moore, 1997] and parents were encouraged to “wait and see,” despite parents’ identification of concerns by at least age 2. It is critical that professionals recognize parents’ early concerns and facilitate accurate diagnosis and treatment [Quality Standards Subcommittee of the Ameri-

can Academy of Neurology and the Child Neurology Society, 2000], in order to provide accurate answers for parents’ concerns and questions and to facilitate early intervention. Intervention (discussed below) appears to be most effective when it occurs by age 3 or earlier; furthermore, interventions for ASD versus general developmental delay differ significantly, another reason for accurate and specific early diagnosis of ASD.

Over the past decade, long-term outcomes have improved for many children, particularly those diagnosed at an early age and receiving early intervention. This holds true despite the relatively greater uncertainty of diagnoses at earlier ages. The earlier services are begun (ideally, prior to 18 months) the better the outcomes are for language skills, social abilities, decreased frustration, and incidents of aggression. Findings indicate that the most important factors are timing (the earlier, the better) and tailoring a program specifically to a given child’s needs, interests, and abilities, rather than participation in any given program [Rogers, 2001]. Because of the somewhat lower accuracy of earlier diagnosis, early mislabeling can give rise to more optimistic outcomes if nonautistic children are included in a research sample. However, the individual benefits of early intervention seem to outweigh the risks of inaccurate diagnosis.

### Etiology

There is clear evidence that autism is a disorder with a significant genetic component [see Cook, 1998, for a review]. Specifically, autism clusters in families [Jorde et al., 1990], and family studies demonstrate an increased risk of autism in first-degree relatives of affected individuals [e.g., sibship recurrence is estimated at 3%; Piven and Palmer, 1999]. Studies have also demonstrated increased rates of sub-clinical autistic symptomatology (the Broader Autism Phenotype), such as an increase of 15–20% in cognitive impairments in siblings of probands, and of 20% for the broader phenotype in siblings. Research also indicates a role for environmental factors; monozygotic twins do not necessarily both develop autism despite identical gene complements. Despite numerous studies demonstrating effects of both genetic and environmental factors, summarized in Table 1, there is to date no definitive solution to the puzzle of the etiology of ASD.

## NEUROBIOLOGY OF AUTISM

The neuroanatomy and neural functioning of autism has increasingly been studied in recent years due to the multiplication of new (and particularly noninvasive) methodologies. These include computerized tomography (CT), magnetic resonance imaging (MRI), functional MRI, positron emission tomography (PET), single photon emission computed tomography (SPECT), heart rate, galvanic skin response, evoked response potential (ERP) electrophysiological techniques, and research on psychopharmacological interventions. See Kennedy et al. and Davidson et al. [current issue] for overviews of these methods. Table 2 provides a summary of neurobiological findings.

### Cerebellar Abnormality

In general, both CT and MRI data indicate an absence of gross structural brain lesions in ASD. The most consistent neuropathologic finding (from autopsy studies) is a paucity of cerebellar Purkinje cells [Bailey et al., 1998]. Although sample sizes are small, data indicate that the neurons of the deep cerebellar nuclei and the inferior olive are atypical in autism, likely due to abnormalities in cells to which they project or in their input. These studies also demonstrate abnormally small, densely packed neurons in the forebrain (hippocampus, amygdala, entorhinal cortex), consistent with arrested development [Bauman and Kemper, 1994]. There have been numerous subsequent studies of the posterior fossa area (the cerebellum, pons, and fourth ventricle). Some reports suggest decreased cerebellar volume as well as a smaller ratio of cerebellum to posterior fossa and cerebellum to total brain [Gaffney et al., 1987]; smaller area of pons [Gaffney et al., 1988]; smaller ratio of cerebellar lobules VI–VII to I–V [Courchesne et al., 1988]; and a smaller volume of cerebellar hemispheres [Murakami et al., 1989]. However, these findings of decreased cerebellar volume have not been replicated [Garber and Ritvo, 1992; Holttum et al., 1992], and data suggest that cerebellar hypoplasia may be secondary to IQ differences, not specific to autism [Piven et al., 1997; Schaefer et al., 1996]. Thus, while cerebellar anomalies appear to play a role in the disorder, they are likely one facet of a complex set of neural differences.

### White Matter Tracts

The corpus callosum, the largest and most prominent axonal pathway in

**Table 1. Possible Etiologies of Autism Spectrum Disorders**

Approach	Suggested Mechanism	Notes	Reference(s)
Genetic mechanisms and inheritance			
Imprinting	Differential gene expression from chromosomes of different parental origin		Skuse, 2000
Mosaicism	Error during embryonic cell division impedes segregation of chromosomes or creates mutation		Discussed in Pearson, 2002
Environmental factors			
Genetic liability combined with an environmental insult	Prenatal exposure to toxin (e.g., thalidomide)		Rodier, 1994; Stromland et al., 1994
Prenatal stress	Possible increase of prenatal stressors for children later diagnosed with ASD	Not replicated by Piven et al., 1993	Beversdorf et al., unpublished data
Sub-optimal uterine environment	Lowered maternal dopamine beta-hydroxylase results in a lower norepinephrine: dopamine ratio		Robinson et al., 2001
Prolonged perceptual and social deprivation	11 of 165 children adopted from Romanian orphanages exhibited symptoms of autism	6 children remitted fully	Rutter et al., 1999
Genomic screen studies			
Candidate genes/regions	5-hydroxytryptamine transporter gene; Dopamine $\beta$ -hydroxylase gene; GLUR6 gene on 6q21; 15q11–13; 7q22–31 region; FOXP2 gene		Reviewed in Folstein et al., 2001
Overlapping expression of craniofacial, neural genes	HOX A1 area	Not replicated in Li et al., 2002.	Rodier et al., 1997; Rodier et al., 1996
Epidemiological, screening studies			
Genes suggested by associations between ASD and genetic disorders	Down syndrome; Turner's syndrome; Fragile X syndrome; Phenylketonuria (PKU); Tuberculous sclerosis; X;8 translocation; 20p deletion on 18	Weaker when dysmorphology, MR excluded	Review: Cook, 1998
Twin studies	Concordance rate in twins: 70% MZ, 0% DZ; 80% MZ concordance for Broader Phenotype	Data suggest 2–5 genes in action	Bailey et al., 1995; Pickles et al., 1995; Ritvo et al., 1985
Autoimmune and infectious origins of autism			
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)	For PANDAS patients with OCD and tic disorders, sudden onset or acute exacerbation of symptoms following streptococcus infection. Similarities noted for cases of ASD	No direct evidence regarding etiology	Swedo et al., 1998
Immune system dysfunction	Increased auto-antibodies or other immune system differences	Data not specific to ASD	Gupta, 2000; Zimmerman, 2000
Measles-mumps-rubella (MMR) vaccine	Hypothetical link between MMR and autism posited in uncontrolled study	Findings not replicated	Fombonne & Chakrabarti, 2001
Prenatal maternal rubella infection	Large sample of children exposed prenatally to rubella later diagnosed with ASD		Chess, 1977; Frey, 1997
Autoimmune system dysfunction	Atypical configuration of histocompatibility antigens locus suggests autoimmune deficits		Hornig & Lipkin, 2001

the brain, is responsible for inter-hemispheric transfer of information. MRI studies suggest significantly decreased size of the body and posterior regions of the callosum in autism [Piven et al., 1997], indicating less effective interhemispheric communication. A “disconnection” of the two hemispheres could theoretically account for some symptoms of ASD [Ellis et al., 1994]. Diffusion tensor imaging (DTI) methods such as those described by Watts et al. [this issue] may provide a better understanding of how these fiber tracts and others involving prefrontal circuitry may be disrupted in ASD.

### Temporal Lobe Abnormality

The limbic system has been a focus of investigation in autism, based on symptom presentation and the finding of amygdala and other forebrain abnormalities. The amygdala may be critical in modulating the learning of nuances of

social interactions [Prather et al., 2001]. Lesions of the amygdala, given early in development to macaque monkeys, have been proposed as an animal model of autism, as they lead to autism-like symptomatology [Bachevalier, 1994]. Based on the social deficits characteristic of autism, MRI studies of the amygdala and related structures have demonstrated bilaterally enlarged amygdala volumes in high-functioning individuals with autism [Howard et al., 2000]. In contrast, other reports indicate decreased volumes in anterior limbic areas (right paracingulate sulcus, left inferior frontal gyrus) and increases in posterior areas (amygdala, middle temporal gyrus, inferior temporal gyrus), and in regions of the cerebellum [Abell et al., 1999]. One MRI study of a pair of MZ twins demonstrated decreased caudate, amygdala, and hippocampus volumes, as well as smaller cerebellar vermis lobules VI and VII, as well as

reduced volumes of the superior temporal gyrus and the frontal lobe relative to controls [Kates et al., 1998]. Anatomical studies of the limbic system are generally consistent with incomplete pruning early in development (arrested development).

To better understand the atypical memory abilities in ASD, investigators have examined the temporal lobes and ventricular system. One early study found enlargements of the left temporal horn of the lateral ventricle [Hauser, DeLong, and Rosman, 1975], suggesting decreased volumes of surrounding structures, particularly the temporal lobes. More recently, abnormalities of the ventricular system in autism have been reported, although samples were heterogeneous and included individuals with neurological conditions [Damasio et al., 1980; Gillberg and Svendsen, 1983].

**Table 2. Imaging Studies of Autism Spectrum Disorders**

Autism Group	Control Group (s)	Methodology	Findings <sup>1</sup>	Reference(s)
22 male adults	20 male controls	volumetric MRI	Greater total brain, total tissue, lateral ventricle volumes	Piven et al., 1996
16 non-MR adults; 22 males	41 age-matched controls	volumetric MRI	Increased volume of cerebellum, cerebellar hemispheres	Hardan et al., 2001b
35 subjects (mean: 18 years)	36 healthy controls matched on age, IQ	volumetric MRI	Increased volume of parietal, temporal, and occipital lobes, overall brain size; decreased callosal volume	Piven et al., 1996, 1997
9 individuals	9 controls	volumetric MRI	Minicolumnar abnormalities in frontal, temporal lobes	Casanova et al., 2002
13 non-MR adults	35 control scans	volumetric MRI	Enlarged fourth ventricle	Gaffney et al., 1987
16 non-MR adults	19 male adults	volumetric MRI	Increased cerebral and third ventricle volumes	Hardan et al., 2001a
13 non-MR boys (mean: 11 years)	35 archival MRI scans (unmatched)	volumetric MRI	Reduced brainstem, particularly the pons.	Gaffney et al., 1988
29 children	15 controls	volumetric MRI	Decreased brainstem volume	Hashimoto et al., 1992
13 non-MR boys (mean: 11 years)	35 archival MRI scans (unmatched)	volumetric MRI	Bilaterally enlarged amygdala	Howard et al., 2000
15 non-MR individuals	15 age- and IQ-matched controls	volumetric MRI	Decreased volume of paracingulate sulcus, inferior frontal gyrus; increases in amygdala, middle temporal gyrus, inferior temporal gyrus, cerebellum	Abell et al., 1999
51 individuals (ages 3–42)	51 age-, sex-matched controls	volumetric MRI	Reduced area of corpus callosum regions where parietal areas project	Egaas et al., 1995
Twin pair: one child with autism	Sibling with sub-clinical symptoms	volumetric MRI	Reduced volume of caudate, amygdala, hippocampus; cerebellum; superior temporal gyrus; frontal lobes	Kates et al., 1998
16 non-MR boys (ages 7–11)	15 age-matched controls	volumetric MRI	Asymmetry reversal in frontal language-related cortex; posterior temporal fusiform gyrus more left-sided	Herbert et al., 2002
15 adults	15 controls	volumetric MRI	Reduced volume of the left planum temporale, a language related brain structure	Rojas et al., 2002
38 boys (ages 2–11)	39 age-matched boys	volumetric MRI	Hyperplasia of frontal, temporal, parietal areas in younger children; volume increases over age reduced.	Carper et al., 2002
14 children	14 control children	volumetric MRI	Decreased exploration and rates of stereotyped behaviors correlated with cerebellar hypoplasia	Pierce et al., 2001
21 non-MR adults	24 adults	volumetric MRI	Reduced gray matter in fronto-striatal and cerebellar regions; related to impaired sensorimotor gating	McAlonan et al., 2002
17 patients	17 age-, sex-matched controls	PET: Verbal learning; MRI	Glucose hypometabolism in anterior and posterior cingulate; reduced volume of anterior cingulate gyrus	Haznedar et al., 2000
33 children	10 MR age-, IQ-matched controls	PET: Resting	Hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex	Zilbovicius et al., 2000
5 non-MR adults	5 age-matched adults	PET: sentence processing	Reversed hemispheric dominance for verbal perception; reduced cerebellar activation for nonverbal perception	Mueller et al., 1999
14 non-MR adults	2 groups of 14 normal controls	fMRI: Face identification	Greater inferior temporal gyri and decreased fusiform gyrus activation during face processing	Schulz et al., 2000
8 males	8 controls	fMRI: Finger movement task	Atypical individual variability of functional maps, less distinct regional activation/deactivation patterns	Mueller et al., 2001
11 non-MR adults	6 controls	fMRI: Working memory	Decreased activation in dorsolateral prefrontal cortex and posterior cingulate cortex	Luna et al., 2002
6 non-MR adults	12 age-, IQ-matched controls	fMRI: Social inference task	ASD group activated fronto-temporal regions but not amygdala during inference task	Baron-Cohen et al., 1999
18 children (ages 4–17)	10 age-matched controls	SPECT	Decreased cerebral blood flow in the left hemisphere, particularly in sensorimotor and language-related cortex	Chiron et al., 1995
6 children	6 age-matched controls	SPECT	Temporal and parietal lobes had abnormal regional cerebral blood flow	Mountz et al., 1995
23 children (28–92 months)	None	SPECT, MRI	20 of 23 children had areas of decreased perfusion in cerebellum, thalamic and parietal cortex	Ryu et al., 1999

<sup>1</sup>Unless otherwise noted, findings are reported as differences between autism group as compared with control group(s).

### Frontal Lobes

The frontal lobes are the seat of executive functions, which may be impaired in ASD, as discussed above. MRI

data indicates increased volumes of parietal, temporal, and occipital lobes and overall brain volume enlargements, but no increases for the frontal lobes, com-

pared to normal controls [Piven et al., 1996]. Thus, relative to the rest of the brain, the frontal lobes may be the most abnormal in volume.

## Measures of Brain Volume

Overall brain volume provides a general measure of neural development. Although frank macrocephaly, or brain enlargement, is found in only a small proportion, enlarged head circumference measures have been demonstrated in a significant subset of individuals with ASD [Piven et al., 1995], as have increased cerebral (white matter) volumes [Filipek et al., 1992]. Enlargements may be the consequence of atypical head growth in early and middle childhood [Lainhart et al., 1997]. Excessive white matter connections suggest a failure of cortical pruning early in development, which could lead to “sticky brain networks” that fail to learn readily [Cohen, 1994].

## Functional Neuroanatomy in Autism

The literature on functional brain activity in individuals with ASD is even less consistent than the structural brain literature, with few replicated findings. Electrophysiological studies have demonstrated abnormalities of evoked response potentials (ERPs), specifically, the auditory P300 and P700 and auditory and visual negative components, suggesting deficits in sensory information processing or in the maintenance and shifting of selective attention [Courchesne, 1987] and possibly accounting for the delays in responding often observed in this population. PET studies have indicated abnormal structure and metabolism of the anterior cingulate gyrus [Haznedar et al., 1997]. This finding is consistent with the functional difficulties observed in autism with processing affect, regulated in part by the anterior cingulate.

## Neurochemical Basis of Autism

The literature on development and functioning of neurotransmitter systems in autism is generally focused on two of the transmitters, serotonin and dopamine. Serotonin is important for the role it plays in regulating the processes of neurogenesis, neuronal differentiation, neuropil formation, axon myelination, and synaptogenesis. Neurochemically, the most consistent finding in autism has been an increase in blood serotonin. [Anderson et al., 1990], likely causing a loss of serotonin terminals, which would lead to altered developmental processes such as decreased hippocampal volumes [Aylward et al., 1999]. Brain serotonin synthesis capacity in childhood seems to be disrupted in autism [Chugani et al., 1999]; there are significant differences between prepubertal and postpubertal

children, with the latter having lower serotonin concentrations than the former [McBride et al., 1998], contrary to the typical pattern.

The dopamine system may play a role in mediating the repetitive and stereotypic movements of autism. Functional imaging (using PET) suggested reduced F-fluorodopa (F-DOPA) activity in the anterior medial prefrontal cortex, compared with the occipital cortex, in autism [Ernst et al., 1997]. Findings, which indicated decreased dopaminergic function in prefrontal cortex, could also be related to executive dysfunction in ASD. Furthermore, the dopamine system is critical in the system involving the frontal lobes and the closely related structures of the basal ganglia, medial-temporal lobes, and thalamic nuclei. As discussed, there is substantial evidence of impairment in these systems.

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***“Findings [from both neuroimaging and neurochemical studies] are suggestive of early, neuromodulatory effects rather than of gross or localized abnormalities. . .”***

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## Autonomic Nervous System Functioning

There is relatively little research on low-level autonomic nervous system (ANS) functioning in ASD. Studies of sleep stages, circadian rhythms, and sleep-waking patterns in children with autism have failed to demonstrate clear differences [Yuwiler et al., 1971]. Arousal or “tonic” activation of the ANS is related to functioning of the brainstem reticular formation and catecholaminergic mechanisms; although findings are inconsistent, they do not suggest constant over- or under-arousal in ASD. However, arousal levels (heart rate and skin conductance) may differ in response to auditory stimuli, such that individuals with autism exhibit less reactivity to stimuli with social content [Palkovitz and Wiesenfeld, 1980]. Children with autism seem to have greater autonomic responsiveness to all environmental stimulation,

and this vulnerability to hyperarousal may lead to avoidance or self-stimulatory behaviors [Hirstein et al., 2001]. At least one study has demonstrated convincing evidence of significant autonomic dysregulation and an inability to mobilize processing resources appropriately [Zahn et al., 1987].

## TREATMENT OF AUTISM SPECTRUM DISORDERS

Interventions for individuals with ASD typically involve some combination of special education, behavioral interventions, and pharmacological interventions. Table 3 summarizes findings in the intervention and treatment of ASD. In general, pharmacological strategies are reserved for adolescents and adults, or for specifically targeted symptoms in younger children [Campbell et al., 1996]. Interestingly, the behaviors and symptoms that are most effectively addressed with medication are typically not the core features of autism (social and communicative skills), but rather include aggression, self-injurious behaviors, stereotyped movements, and attentional deficits [Volkmar, 2001].

A relevant consideration in assessing a medication’s efficacy is the mechanism underlying positive outcomes. For example, a medication may reduce inattention, allowing a child to learn more effectively in the classroom and thus increasing academic performance. In this case, the secondary change in academic abilities should be distinguished from direct effects on attentional abilities. In contrast with pharmacological approaches, behavioral treatments have been found to more directly target core symptoms of ASD. While the efficacy of interventions is more difficult to quantify, as changes are long-term and require longitudinal studies, the four primary behavioral interventions summarized in Table 2 have all exhibited some success to date. Finally, in addition to the above approaches, which are either empirically validated or based on an empirical literature, there are a number of “alternative and complementary” therapies that are less evidence-based. Families are invested in exploring alternative therapies in part because the core deficits of ASD have been largely resistant to pharmacological treatments.

## DISCUSSION

Studies using functional and structural MRI, genetic, neurochemical, autonomic system, and autoimmune approaches to ASD indicate several consistent findings, although findings

**Table 3. Treatment of Autism Spectrum Disorders**

Pharmacological Treatments	Efficacy	Mechanism	Effects & Concerns	Reference(s)
Atypical Antipsychotics				
risperidone (Risperdal)	Moderate	Block dopamine and serotonin receptors	↓ tantrums, self-injury, irritability, aggression	Research Units on Pediatric Psychopharmacology Autism Network, 2002
haloperidol (Haldol)	Moderate, with side effects	Dopamine blocker	↓ stereotypies, withdrawal; ↑ dystonia, dyskinesia	Campbell et al., 1978, 1988
Serotonin system				
clomipramine (Anafranil)	Moderate, with side effects	Serotonin reuptake	↓ repetitive thoughts, aggression; ↑ seizures	Gordon et al., 1993
fluvoxamine (Luvox)	Moderate	Serotonin reuptake inhibitor (SSRI)		McDougle et al., 1994
fluoxetine (Prozac)	Moderate	SSRI		Cook et al., 1992
d,l-fenfluramine	Not replicated	Lowers plasma serotonin	Long-term effects possible	Campbell et al., 1988; Ekman et al., 1989; Leventhal et al., 1993
Noradrenergic system				
Beta Blockers	Small number of studies	Blocks adrenaline in beta receptors	↓ aggression and ↑ arousal	Ratey et al., 1987
Behavioral Treatments				
Treatment and Education of Autistic & Related Communication Handicapped Children (TEACCH)	Growing empirical support	Environmental adaptations to deficits (e.g., use of visual cues)	Benefits in core symptoms	Schopler, 1994
Behavior modification: Early Intervention Project (EIP)	Widely implemented, empirical support	Behavior enhancement and reduction techniques via applied behavioral analysis (ABA)	Improvement in core symptoms. Poor generalization to novel settings	McEachin et al., 1993; Gresham & MacMillan, 1997a,b; Schopler et al., 1993
Greenspan approach	No empirical support	Floortime; emotional learning techniques to promote interaction.	Improvement in core symptoms. Parents may feel isolated	Greenspan, 1998
Social skills training	Early results promising	Teach social competence, often in group setting.	Improvement in core symptoms	Dyer & Peck, 1987; Koegel et al., 1994; Lord, 1995
Alternative/Complementary Therapies				
Secretin	Not replicated	Gastrointestinal polypeptide	Unknown	Horvath et al., 1998; Dunn-Geier et al., 2000; Owley et al., 2001
Megavitamins: B6, magnesium	Not replicated		Unknown	Martineau et al., 1988; Rimland, 1988
Restricted diet	Not replicated	Eliminate gluten & lactose from diet	Nutrition	Knivsberg et al., 1990, 1995
Facilitated communication	None	Physical assistance in use of keyboard	Denounced by prof. organizations	Bomba et al., 1996; Smith & Belcher, 1993
Auditory Integration Training	Not replicated	Dampen sound sensitivity	Unknown	Gillberg et al., 1997

across various methodologies have not yet converged to provide a unified hypothesis of the underlying etiology and mechanisms of the disorder. Frontal, medial prefrontal, temporal, and anterior cingulate cortical regions have revealed differences in individuals with autism; subcortical areas of interest have included the amygdala, basal ganglia, thalamus, and cerebellum. Neurochemically, findings are suggestive of early, neuromodulatory effects rather than of gross or localized abnormalities, similar to the structural imaging findings.

Pharmacological interventions for ASD indicate that in general, dopamine

blockers and related compounds are somewhat effective in the treatment of stereotypies and overactivity, and conversely, agents that stimulate dopamine activity (e.g., stimulant medications) typically exacerbate symptoms in autism [Campbell et al., 1972]. In contrast, serotonin is involved in the mediation of a wide range of behaviors and psychological processes, including mood, anxiety, repetitive thoughts, sleep, aggression, impulsivity, and social interaction and affiliation [Whitaker-Azmitia and Peroutka, 1990], and functioning of the serotonin system may be impaired in ASD. Serotonin system drugs have been found to be

more helpful in addressing anxiety-like symptoms.

It is notable that pharmacological approaches in general are atheoretical with respect to the underlying causes of autism; rather, they target global symptoms. One important goal for future studies is to design more specific interventions. Genetic studies are likely to provide an important strategy for developing such targeted pharmacological interventions, although identifying candidate genes is a complex matter. When we can focus on genes that play a role in the etiology of the ASD, researchers will be able to characterize the biochemical ef-

fects of mutations, investigate the molecular effects of mutations on biochemical neural processes, study the effects of mutations via stem cells, study the effects of therapeutic agents on animal models, and develop clinical trials [Cook, 1998]. No single set of findings is conclusive, but the genomic screen approach is promising for the future [Folstein and Rosen-Scheidley, 2001]. The data on interventions highlights the importance of including young children in neurobiological studies of autism. Given the greater neural and behavioral plasticity characteristic of younger individuals, there may be a greater opportunity to find differences that lead to lasting improvements. In addition, the study of younger children avoids the complications introduced by the adaptations and coping mechanisms that older individuals have adopted to cope with the experience of having a disorder. End state behaviors may be secondary adaptations to earlier primary deficits.

The reviewed reports highlight the heterogeneity of approaches and hypotheses for understanding the mechanisms underlying ASD, and to date, there are only a small number of consistent findings. However, the overall picture is a hopeful one, with increasingly positive outcomes possible for many individuals and with a many promising avenues of investigation.

### Linking Research to Behaviors: New Directions

There are several developments in noninvasive neuroimaging and other neurocognitive approaches that present an exciting new challenge for the study of development in ASD. For example, diffusion tensor imaging (DTI) is a technique that permits the tracking of white matter fiber tracts by quantifying the diffusion of water molecules in the brain [see Watts et al., this issue]. Molecules diffuse less readily across membranes, and part of MRI processes facilitates the directional mapping of white matter tracts based on this principle. Applying such a technique in autism would help to explicate any differences in the trajectories and connections of neural tracts between brain areas. Another exciting approach is investigating genetic influences on brain development by correlating well-known genetic polymorphisms with brain morphology and behavior [Casey et al., 2001 and Fosella et al., this issue].

There are a number of limitations of both structural and functional neuroimaging studies that likely play a role in the lack of replicated findings to date. For

morphometric MRI studies, this includes the reliability and validity of measurements (partially resolved by using measurements that rely on whole volumes rather than a single representative slice). Moreover, although group differences in brain volume have been quantified, individual cells and cell layers are not visualized, thus precluding an assessment of the underlying cause of differences in brain shape and volume. Few studies have linked differences in volume of brain regions to clinical symptomatology or severity; this approach would be ideal for exploring the role of neural disruption in symptoms of autism. A significant concern in both structural and fMRI studies has been the appropriate selection of controls and biases in subject selection. Specifically, low-SES populations are frequently not included; and comparison samples have often included patients whose scans have been read as normal. Gender, chronological age, mental age (IQ), body weight, seizures, and some medical conditions contribute to anatomical and functional differences, and behavioral parameters all play a significant role in imaging findings. The selection of controls matched on these parameters is critical. Compounding the difficulty is that imaging requires considerable statistical power, and sample sizes are not necessarily large enough to provide adequate power. Finally, to date it has been difficult to develop imaging paradigms that address core symptoms of autism and demonstrate autism-specific differences in functional activity.

In summary, the study of autism spectrum disorders using noninvasive structural and functional MRI, DTI, genetic approaches, and emerging methodologies offers both the challenge and the promise of understanding the neural underpinnings of ASD and their relationship to the specific strengths and weaknesses characteristic of the broader autism phenotype.

### REFERENCES

Abell F, Krams M, Ashburner J, et al. 1999. The neuroanatomy of autism: A voxel-based whole brain analysis of structural scans. *NeuroReport* 10:1647-1651.

American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders 4th ed.. Washington, DC: American Psychiatric Association.

Anderson GM, Horne WC, Chatterjee D, et al. 1990. The hyperserotonemia of autism. *Ann N Y Acad Sci* 600:331-340.

Aylward EH, Minshew NJ, Goldstein G, et al. 1999. MRI volumes of amygdala and hippocampus in nonmentally retarded autistic adolescents and adults. *Neurology* 53:2145-2150.

Bachevalier J. 1994. Medial temporal lobe structures and autism: A review of clinical and experimental findings. *Neuropsychologia* 32: 627-648.

Bailey A, Bolton P, Butler L, et al. 1993. Prevalence of the fragile X anomaly amongst autistic twins and singletons. *J Child Psychol Psychiatry* 34:673-688.

Bailey A, Le Couteur A, Gottesman I, et al. 1995. Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychol Med* 25:63-77.

Bailey A, Luthert P, Dean A, et al. 1998. A clinicopathological study of autism. *Brain* 121: 889-905.

Baron-Cohen S, Cox A, Baird G, et al. 1996. Psychological markers in the detection of autism in infancy in a large population. *Br J Psychiatry* 168:158-163.

Baron-Cohen S, Leslie A, Frith U. 1985. Does the autistic child have a "theory of mind"? *Cognition* 21:37-36.

Baron-Cohen S, Ring HA, Wheelwright S, et al. 1999. Social intelligence in the normal and autistic brain: an fMRI study. *Eur J Neurosci* 11:1891-1898.

Bartak L, Rutter M, Cox A. 1975. A comparative study of infantile autism and specific developmental language disorder: I. *The Children. Br J Psychiatry* 126:127-145.

Bartolucci G, Albers RJ. 1974. Deictic categories in the language of autistic children. *J Autism Childhood Schizophrenia* 19:131-141.

Bartolucci G, Pierce SJ, Streiner D. 1980. Cross-sectional studies of grammatical morphemes in autistic and mentally retarded children. *J Autism Dev Disord* 10:39-50.

Bauman ML, Kemper TL. 1994. Neuroanatomic observations of the brain in autism. In ML Bauman & TL Kemper Eds., *The neurobiology of autism* pp. 119-145. Baltimore, MD: Johns Hopkins University Press.

Bennetto L, Pennington BF, Rogers SL. 1996. Intact and impaired memory functions in autism. *Child Dev* 67:1816-1835.

Berument SK, Rutter M, Lord C, et al. 1999. Autism screening questionnaire: Diagnostic validity. *Br J Psychiatry* 175:444-451.

Bomba C, O'Donnell L, Markowitz C, et al. 1996. Evaluating the impact of facilitated communication on the communicative competence of fourteen students with autism. *J Autism Dev Disord* 26:43-58.

Bryson S. 1996. Brief report: Epidemiology of autism. *J Autism Dev Disord* 26:165-168.

Bryson SE, Clark BS, Smith TM. 1988. First report of a Canadian epidemiological study of autistic syndromes. *J Child Psychol Psychiatry* 29: 433-445.

Campbell M, Fish B, David R, et al. 1972. Response to triiodothyronine and dextroamphetamine: A study of preschool schizophrenic children. *J Autism Child Schizophr* 2:343-358.

Campbell M, Anderson LT, Meier M, et al. 1978. A comparison of haloperidol and behavior therapy and their interaction in autism. *J Am Acad Child Adolesc Psychiatry* 17:640-655.

Campbell M, Adams P, Perry R, et al. 1988a. Tardive and withdrawal dyskinesia in autistic children. *Psychopharmacol Bull* 24:251-255.

Campbell M, Adams P, Small AM, et al. 1988b. Efficacy and safety of fenfluramine in autistic children. *J Am Acad Child Adolesc Psychiatry* 27:434-439.

Campbell M, Schopler E, Cueva JE, et al. 1996. Treatment of autistic disorder. *J Am Acad Child Adolesc Psychiatry* 35:134-143.

- Carper RA, Moses P, Tigue ZD, et al. 2002. Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage* 16: 1038–1051.
- Casanova MF, Buxhoeveden DP, Switala AE, et al. 2002. Minicolumnar pathology in autism. *Neurology* 58: 428–432.
- Casey BJ, Durston S, Fossella JA. 2001. Evidence for a mechanistic model of cognitive control. *Clin Neurosci Res* 1:267–282.
- Chess S. 1977. Follow-up on autism in congenital rubella. *J Autism Child Schizophr* 7:69–81.
- Chiron C, Leboyer M, Leon F, et al. 1995. SPECT of the brain in childhood autism: evidence for a lack of normal hemispheric asymmetry. *Dev Med Child Neurol* 37: 849–880.
- Chugani DC, Muzik O, Behen M, et al. 1999. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol* 45:287–295.
- Cicchetti D, Rogosch F. 1996. Developmental pathways: Diversity in process and outcome. *Dev Psychopathol* 8:597–606.
- Cohen IL. 1994. Artificial neural network analogue of learning in autism. *Biol Psychiatry* 36:5–20.
- Cook EH. 1998. Genetics of autism. *Ment Retard Dev Disabil Res Rev* 4:113–120.
- Courchesne E. 1987. A neurophysiological view of autism. In E. Schopler & G. Mesibov Eds., *Neurobiological issues in autism* pp. 285–323. New York: Plenum.
- Courchesne E, Yeung-Courchesne R, Press AG, et al. 1988. Hypoplasia of cerebellar lobules VI & VII in infantile autism. *N Engl J Med* 318:1349–1354.
- Dahlgren SO, Gillberg C. 1989. Symptoms in the first two years of life: A preliminary population study of infantile autism. *Eur Arch Psychiatry Neurol Sci* 283:169–174.
- Dalgleish B. 1975. Cognitive processing and linguistic reference in autistic children. *J Autism Dev Disord* 5:353–361.
- Damasio H, Maurer RG, Damasio AR, et al. 1980. Computerized tomographic scan findings in patients with autistic behavior. *Arch Neurol* 37:504–510.
- Davidson MC, Thomas KM, Casey BJ. 2003. Imaging the developing brain with fMRI. *Ment Retard Dev Disabil Res Rev* 9:161–167.
- Dawson G, Lewy A. 1989. Arousal, attention, and the socio-emotional impairments of individuals with autism. In G. Dawson Ed., *Autism: Nature, Diagnosis, and Treatment* pp. 49–74. New York, NY: Guilford Press.
- Dawson G, Meltzoff AN, Osterling J, et al. 1998. Neuropsychological correlates of early symptoms of autism. *Child Dev* 69:1276–1285.
- Dunn-Geier J, Ho HH, Auersperg E, et al. 2000. Effect of secretin on children with autism: A randomized controlled trial. *Dev Med Child Neurol* 42:796–802.
- Dyer K, Peck CA. 1987. Current perspectives on social/communication curricula for students with autism and severe handicaps. *Education and Treatment of Children* 10:338–351.
- Egaas B, Courchesne E, Saitoh O. 1995. Reduced size of corpus callosum in autism. *Arch Neurology* 52:794–801.
- Eisenberg L. 1957. The fathers of autistic children. *Am J Orthopsychiatry* 127:715–724.
- Ekman G, Miranda-Linne F, Gillberg C, et al. 1989. Fenfluramine treatment of twenty children with autism. *J Autism Dev Disord* 19: 511–532.
- Ellis HD, Ellis DM, Fraser W, et al. 1994. A preliminary study of right hemisphere cognitive deficits and impaired social judgments among young people with Asperger syndrome. *Eur Child Adolesc Psychiatry* 3:255–266.
- Ernst M, Zametkin A, Matochik J, et al. 1997. Low medial prefrontal dopaminergic activity in autistic children. *Lancet* 350:638.
- Filipek PA, Richelme C, Kennedy DN. 1992. Morphometric analysis of the brain in developmental language disorders and autism. *Ann Neurol* 32:475.
- Folstein SE, Rosen-Scheidley B. 2001. Genetics of autism: Complex aetiology for a heterogeneous disorder. *Nature Reviews: Genetics* 2:943–955.
- Fombonne E. 1999. Epidemiology of autism: A review. *Psychol Med* 29:769–786.
- Fombonne E, Bolton P, Prior J, et al. 1997. A family study of autism: Cognitive patterns & levels in parents and siblings. *J Child Psychol Psychiatry* 38:667–683.
- Fombonne E, Chakrabarti S. 2001. No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics* 108:1–8.
- Fossella JA, Sommer T, Fan J, et al. 2003. Synaptogenesis and heritable aspects of executive attention. *Ment Retard Dev Disabil Res Rev* 9:000–000.
- Frey TK. 1997. Neurobiological aspects of rubella virus infection. *Intervirol* 40:167–175.
- Frith U, Happe F. 1994. Autism: Beyond “theory of mind”. *Cognition* 50:115–132.
- Gaffney GR, Kuperman S, Tsai LY, et al. 1988. Morphological evidence for brainstem involvement in infantile autism. *Biol Psychiatry* 24:578–586.
- Gaffney GR, Kuperman S, Tsai LY, et al. 1987. Midsagittal magnetic resonance imaging of autism. *Br J Psychiatry* 151:831–833.
- Garber HJ, Ritvo ER. 1992. Magnetic resonance imaging of the posterior fossa in autistic adults. *Am J Psychiatry* 149:245–247.
- Gillberg C, Svendsen P. 1983. Childhood psychosis and computed tomography brain scan findings. *J Autism Dev Disord* 13:19–32.
- Gillberg IC, Gillberg C, Ahlsen G. 1994. Autistic behavior and attention deficits in tuberous sclerosis: A population-based study. *Dev Med Child Neurol* 36:50–56.
- Gillberg C, Johansson M, Steffenburg S, et al. 1997. Auditory integration training in children with autism. *Autism* 1:97–100.
- Gordon CT, State RC, Nelson JE, et al. 1993. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* 50:441–447.
- Griffith EM, Pennington B, Wehner EA. 1999. Executive functions in young children with autism. *Child Dev* 70:817–832.
- Gupta S. 2000. Immunological treatments for autism. *J Autism Dev Disord* 30:475–479.
- Happe F, Frith U. 1996. The neuropsychology of autism. *Brain* 119:1377–1400.
- Hardan AY, Minshew NJ, Mallikarjunn M, et al. 2001a. Brain volume in autism. *J Child Neurol* 16:421–424.
- Hardan AY, Minshew NJ, Harenski K, et al. 2001b. Posterior fossa magnetic resonance imaging in autism. *J Am Acad Child Adolesc Psychiatry* 40:666–672.
- Hashimoto T, Tayama M, Miyazaki M, et al. 1992. Reduced brainstem size in children with autism. *Brain Dev* 14: 94–97.
- Hauser SL, DeLong GR, Rosman NP. 1975. Pneumographic findings in the infantile autism syndrome: A correlation with temporal lobe disease. *Brain* 98:667–688.
- Haznedar MM, Buchsbaum MS, Metzger M. 1997. metabolism in autistic disorder. *Am J Psychiatry* 154:1047–1050.
- Haznedar MM, Buchsbaum MS, Wei TC, et al. 2000. Limbic circuitry in patients with autism spectrum disorders studied with PET and MRI. *Am J Psychiatry* 157:12:1994–2001.
- Herbert MR, Harris GJ, Adrien KT, et al. 2002. Abnormal asymmetry in language association cortex in autism. *Ann Neurol* 52:588–596.
- Hirstein W, Iverson P, Ramachandran VS. 2001. Autonomic responses of autistic children to people and objects. *Proc R Soc Lond B Biol Sci* 268:1883–1888.
- Hobson RP. 1986. The autistic child’s appraisal of expressions of emotion. *J Child Psychol Psychiatry* 27:321–342.
- Holttun JR, Minshew NJ, Sanders RS, et al. 1992. Magnetic resonance imaging of the posterior fossa in autism. *Biol Psychiatry* 32:1091–1101.
- Hornig M, Lipkin WI. 2001. Infectious and immune factors in the pathogenesis of neurodevelopmental disorders: epidemiology, hypotheses, and animal models. *Ment Retard Dev Disabil Res Rev* 7:200–210.
- Horvath K, Stefanatos G, Sokolski KN, et al. 1998. Improved social and language skills after secretin administration in autistic spectrum disorders. *J Assoc Acad Minor Phys* 9:9–15.
- Howard MA, Cowell PE, Boucher J, et al. 2000. Convergent neuroanatomical and behavioral evidence of an amygdala hypothesis of autism. *NeuroReport* 11:2931–2935.
- Howlin P. 1984. The acquisition of grammatical morphemes in autistic children: Critique and replication of Bartolucci, Pierce, and Streiner, 1980. *J Autism Dev Disord* 14:127–136.
- Howlin P, Moore A. 1997. Diagnosis of autism: Survey of 1200 UK patients. *Autism* 1:135–162.
- Hughes C, Leboyer M, Bouvard M. 1997. Executive function in parents of children with autism. *Psychol Med* 27:209–220.
- Hughes C, Plumet MH, Leboyer M. 1999. Towards a cognitive phenotype for autism: Increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. *J Child Psychol Psychiatry* 40:705–718.
- Jorde LB, Mason-Brothers A, Waldmann R, et al. 1990. The UCLA-University of Utah epidemiological survey of autism: Genealogical analysis of familial aggregation. *Am J Med Genet* 36:85–88.
- Kates WR, Mostofsky SH, Zimmerman AW, et al. 1998. Neuroanatomical & neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. *Ann Neurol* 43:782–791.
- Kennedy DN, Haselgrove C, McInerney S. 2003. MRI-based morphometric of typical and atypical brain development. *Ment Retard Dev Disabil Res Rev* 9:000–000.
- Knivsberg AM, Wiig K, Lind G, et al. 1990. Dietary intervention in autistic syndromes. *Brain Dysfunction* 3:315–327.
- Knivsberg AM, Reichelt KL, Nodland M, et al. 1995. Autistic syndromes and diet: A follow-up study. *Scandinavian J Educ Res* 39: 223–236.
- Koegel RL, Frea WD, Surratt AV. 1994. Self-management of problematic social behavior. In E. Schopler & G. Mesibov Eds., *Behavioral Issues in Autism* pp. 81–94. NY: Plenum.
- Lainhart JE, Piven J, Wzorek M, et al. 1997. Macrocephaly in children & adults with autism. *J Am Acad Child Adolesc Psychiatry* 36:282–290.
- Landa R, Folstein SE, Isaacs C. 1991. Spontaneous narrative-discourse performance of parents of

- autistic individuals. *J Speech Hear Res* 34: 1339–1345.
- Landa R, Piven J, Wzorek MM, et al. 1992. Social language use in parents of autistic individuals. *Psychol Med* 22:245–254.
- Leboyer M, Phillippe A, Bouvard M, et al. 1999. Whole blood serotonin and plasma beta-endorphin in autistic probands and first-degree relatives. *Biol Psychiatry* 45:158–163.
- Leventhal BL, Cook EH, Morford M, et al. 1993. Clinical and neurochemical effects of fenfluramine in children with autism. *J Neuropsychiatry Clin Neurosci* 5:307–315.
- Li J, Tabor H, Nguyen L, et al. 2002. Lack of association between HoxA1 and HoxB1 gene variants and autism in 110 multiplex families. *Am J Med Genetics* 114:24–30.
- Lord C. 1995. Facilitating social inclusion. In E. Schopler & G. Mesibov Eds., *Learning and Cognition in autism* pp. 221–39. New York: Plenum Press.
- Lord C, Paul R. 1997. Language and communication in autism. In Cohen & Volkmar Eds., *Handbook of autism & pervasive developmental disorders* pp. 195–225. New York: Wiley.
- Lord C, Pickles A. 1996. Language level and non-verbal social-communicative behaviors in autistic and language-delayed children. *J Am Acad Child Adolesc Psychiatry* 35:1542–1550.
- Lord C, Risi S. 2000. Diagnosis of autism spectrum disorders in young children. In A. M. Wetherby & B. M. Prizant Eds., *Autism spectrum disorders: A transactional developmental perspective* pp. 11–30. Baltimore, MD: Brookes.
- Lord C, Goode S, Heemsbergen J, et al. 1989. Autism Diagnostic Observation Schedule: A standardized observation of communicative and social behavior. *J Autism Dev Disord* 19:185–212.
- Lord C, Rutter M, LeCouteur A. 1994. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 24: 659–685.
- Luna B, Minschew NJ, Garver KE, et al. 2002. Neocortical system abnormalities in autism: an fMRI study of spatial working memory. *Neurology* 59:834–840.
- Martineau J, Bruneau N, Muh JP, et al. 1988. Clinical and biological effects of pyridoxine plus magnesium in autistic subjects. In J. E. Leklum & R. Reynolds Eds., *Clinical and Physiological Applications of Vitamin B6* pp. 329–56. New York: Liss.
- Mawhood L, Howlin P, Rutter M. 2000. Autism and developmental receptive language disorder—A comparative follow-up in early adult life. I: Cognitive and language outcomes. *J Child Psychol Psychiatry* 41: 547–559.
- McAlonan GM, Daly E, Kumari V, et al. 2002. Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain* 125:1594–1606.
- McArthur D, Adamson LB. 1996. Joint attention in preverbal children: Autism and developmental language disorder. *J Autism Dev Disord* 26:481–496.
- McBride PA, Anderson GM, Shapiro T. 1996. Autism research: Bringing together approaches to pull apart the disorder. *Archives of General Psychiatry* 53:980–983.
- McBride PA, Anderson GM, Hertzog ME, et al. 1998. Effects of diagnosis, race, and puberty on platelet serotonin levels in autism and mental retardation. *J Am Acad Child Adolesc Psychiatry* 37:767–776.
- McDougle CJ, Naylor ST, Volkmar FR, et al. 1994. A double-blind, placebo-controlled investigation of fluvoxamine in adults with autism. *Society for Neuroscience Abstracts* 20: 396.
- McEachin JJ, Smith T, Lovaas IO. 1993. Long-term outcomes for children with autism with early intensive behavioral treatment. *American Journal on Mental Retardation* 97:359–372.
- Meltzoff AN. 1988. Infant imitation and memory: Nine-month-olds in immediate and deferred tests. *Child Dev* 59:217–225.
- Minschew N, Goldstein G, Siegel DJ. 1995. Speech and language in high-functioning autistic individuals. *Neuropsychology* 9:255–261.
- Mountz JM, Tolbert LC, Lill DW, et al. 1995. Functional deficits in autism: characterization by technetium-99m-HMPAO and SPECT. *J Nuclear Med* 36:1156–1162.
- Mueller RA, Behen ME, Rothermel RD, et al. 1999. Brain mapping of language and auditory perception in high-functioning autistic adults: A PET study. *J Autism Dev Disord* 29:19–31.
- Mueller RA, Pierce K, Ambrose JB, et al. 2001. Atypical patterns of cerebral motor activation in autism: functional magnetic resonance study. *Bio Psychiatry* 49:665–676.
- Mundy P, Markus J. 1997. On the nature of the communication and language impairment in autism. *Ment Retard Dev Disabil Res Rev* 3:343–349.
- Mundy P, Sigman M, Kasari C. 1990. A longitudinal study of joint attention and language development in autistic children. *J Autism Dev Disord* 20:115–128.
- Murakami JW, Courchesne E, Press GA, et al. 1989. Reduced cerebellar hemisphere and its relationship to vermal hypoplasia in autism. *Arch Neurol* 46:689–694.
- Owley T, McMahon W, Cook EH, et al. 2001. Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. *J Am Acad Child Adolesc Psychiatry* 40:1293–1299.
- Palkovitz RJ, Wiesenfeld AR. 1980. Differential autonomic responses of autistic and normal children. *J Autism Dev Disord* 10:347–360.
- Pearson S. 2002. Human genetics: Dual identities. *Nature* 417:10–11.
- Pickles A, Bolton P, Macdonald H, et al. 1995. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: A twin and family history study of autism. *Am J Hum Genet* 57:717–726.
- Pickles A, Starr E, Kazak S, et al. 2000. Variable expression of the broader autism phenotype: Findings from extended pedigrees. *J Child Psychol Psychiatry* 41:491–502.
- Pierce K, Courchesne E. 2001. Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism. *Biol Psychiatry* 49:655–664.
- Piven J, Palmer P. 1999. Psychiatric disorder and the Broad Autism Phenotype: Evidence from a family study of multiple-incidence autism families. *The Am J Psychiatry*, 156, 557.
- Piven J, Simon J, Chase GA, et al. 1993. The etiology of autism: Pre-, peri-, and neonatal factors. *J Am Acad Child Adolesc Psychiatry* 32:1256–1263.
- Piven J, Arndt S, Bailey J, et al. 1995. An MRI study of brain size in autism. *American Journal of Psychiatry* 152:1145–1149.
- Piven J, Arndt S, Bailey J, et al. 1996. Regional brain enlargement in autism: A magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 35:530–536.
- Piven J, Bailey J, Ranson BJ, et al. 1997a. An MRI study of the corpus callosum in autism. *Am J Psychiatry* 154:1051–1056.
- Piven J, Saliba K, Bailey J, et al. 1997b. An MRI study of autism: The cerebellum revisited. *Neurology* 49:546–551.
- Prather MD, Lavanex P, Mauldin-Jourdain ML, et al. 2001. Increased social fear and decreased fear of objects in monkeys with neonatal amygdala lesions. *Neuroscience* 106:653–658.
- Quality Standards Subcommittee of the American Academy of Neurology & the Child Neurology Society. 2000. Practice parameter: Screening & diagnosis of autism. *Neurology* 55:468–479.
- Rapin I. 1996. Preschool children with inadequate communication: Developmental language disorders, autism, low IQ pp. 58–97. London: MacKeith Press.
- Ratey JJ, Bemporad J, Sorgi P, et al. 1987. Open trial effects of beta-blockers on speech and social behaviors in 8 autistic adults. *J Autism Dev Disord* 17:439–446.
- Research Units on Pediatric Psychopharmacology Autism Network. 2002. Risperidone in children with autism and behavioral problems. *N Engl J Med* 347:314–321.
- Rimland B. 1988. Controversies in the treatment of autistic children: Vitamin and drug therapy. *J Child Neurol* 3: S68–72.
- Ritvo ER, Freeman BJ, Mason-Brothers A, et al. 1985. Concordance for the syndrome of autism in 40 pairs of afflicted twins. *American Journal of Psychiatry* 142:74–77.
- Robinson PD, Schutz CK, Macciardi F, et al. 2001. Genetically determined low maternal serum dopamine beta-hydroxylase levels and the etiology of autism spectrum disorders. *Am J Med Genet* 100:30–36.
- Rodier PM. 1994. Vulnerable periods and processes during central nervous system development. *Environmental Health Perspectives*, 102:121–124.
- Rodier PM, Ingram JL, Tisdale B, et al. 1996. Embryological origin for autism: Developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology* 370:247–261.
- Rodier PM, Ingram JL, Tisdale B, et al. 1997. Linking etiologies in humans and animal models: Studies of autism. *Reproductive Toxicology* 11:417–422.
- Rogers SJ. 2001. Diagnosis of autism before the age of 3. *Int Rev Res Ment Retard* 23:1–31.
- Rogers SJ, Pennington BF. 1991. A theoretical approach to the deficits in infantile autism. *Dev Psychopathol* 3:13–16.
- Rogers SJ, Bennetto L, McEvoy R, et al. 1996. Imitation and pantomime in high-functioning adolescents with autism. *Child Dev* 67: 2060–2073.
- Rojas DC, Bawn SD, Benkers TL, et al. 2002. Smaller left hemisphere planum temporale in adults with autistic disorder. *Neurosci Letters* 328:237–240.
- Rossi PG, Parmeggiani A, Bach V, et al. 1995. EEG features and epilepsy in patients with autism. *Brain Development* 17:169–174.
- Russell J, Jarrold C, Henry L. 1996. Working memory in children with autism and moderate learning difficulties. *J Child Psychol Psychiatry* 37:673–686.
- Rutter M. 1970. Autistic children: Infancy to adulthood. *Seminars Psychiatry* 2:435–450.
- Rutter M, Mawhood L, Howlin P. 1992. Language delay and social development. In P Fletcher & D Hall Eds., *Specific speech and language*

- disorders in children: Correlates, characteristics, and outcomes pp. 63–78. London: Whurr.
- Rutter M, Anderson-Wood L, Beckett C, et al. 1999. Quasi-autistic patterns following severe early global privation. *J Child Psychol Psychiatry* 40:537–549.
- Ryu YH, Lee JD, Yoon PH, et al. 1999. Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: Comparison with findings on MRI. *Eur J Nuclear Med* 26:253–259.
- Schaefer GB, Thompson JN, Bodensteiner JB, et al. 1996. Hypoplasia of the cerebellar vermis in neurogenetic syndromes. *Ann Neurol* 39:382–385.
- Schopler E. 1994. A statewide program for the treatment and education of autistic and related communication handicapped children TEACCH. *Child Adolesc Psychiat Clin N Am* 3:91.
- Schopler E, Reichler RJ, Renner BR. 1988. *The Childhood Autism Rating Scale*. Los Angeles: Western Psychological Services.
- Schopler E, Van Bourgondien ME, & Bristol MM. 1993. *Preschool issues in autism*. NY: Plenum.
- Shapiro T. 1977. The quest for a linguistic model to study the speech of autistic children: Studies on echoing. *J Amer Acad Child Psychiat* 16: 608–619.
- Skuse DH. 2000. Imprinting, the X chromosome, and the male brain: Explaining sex differences in the liability to autism. *Pediatr Res* 47:9–16.
- Smith MD, Belcher RG. 1993. Brief report: Facilitated communication with adults in autism. *J Autism Dev Disord* 23:175–183.
- Stone WL, Hogan KL. 1993. A structured parent interview for identifying young children with autism. *J Autism Dev Disord* 23:639–652.
- Stromland K, Nordin V, Miller M, et al. 1994. Autism in thalidomide embryopathy: A population study. *Dev Med Child Neurol* 36: 351–356.
- Swedo SE, Leonard HL, Garvey M, et al. 1998. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections PANDAS: Clinical description of the first 50 cases. *Am J Psychiatry* 155:264–271.
- Townsend J, Harris NS, Courchesne E. 1996. Visual attention abnormalities in autism: Delayed orienting to location. *J Int Neuropsychol Soc* 2:541–550.
- Volkmar FR. 2001. Pharmacological interventions in autism: Theoretical and practical issues. *J Clin Child Psychol* 30:80–87.
- Volkmar FR, Lord C. 1998. Diagnosis and definition of autism and other pervasive developmental disorders. In F. R. Volkmar Ed., *Autism and pervasive developmental disorders* pp. 1–31. Cambridge, England: Cambridge University Press.
- Volkmar FR, Klin A, Siegel B, et al. 1994. Field trial for autistic disorder in DSM-IV. *Am J Psychiatry* 151:1361–1367.
- Watts R, Liston C, Niogi S, et al. 2003. Fiber tracking using magnetic resonance diffusion tensor imaging and its applications to human brain development. *Ment Retard Dev Disabil Res Rev* 9:168–177.
- Whitaker-Azmitia PM, Peroutka SJ, eds. 1990. *The Neuropharmacology of Serotonin*. New York, NY: New York Academy of Sciences.
- Wolff S, Narayan S, Moyes B. 1988. Personality characteristics of parents of autistic children: A controlled study. *J Child Psychol Psychiatry* 29:143–153.
- Yuwiler A, Ritvo ER, Bald D, et al. 1971. Examination of circadian rhythmicity of blood serotonin and platelets in autistic and nonautistic children. *J Autism Child Schizophr* 1:421–435.
- Zahn TP, Rumsey JM, Van Kammen DP. 1987. Autonomic nervous system activity in autistic, schizophrenic, normal men: Stimulus significance. *J Abnorm Psychol* 96:135–144.
- Zilbovicius M, Boddaert N, Belin P, et al. 2000. Temporal lobe dysfunction in childhood autism: a PET study. *Am J Psychiatry* 157: 1988–1993.
- Zimmerman AW. 2000. Commentary: Immunological treatments for autism: In search of reasons for promising approaches. *J Autism Dev Disord* 30:481–484.