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Autism Spectrum Disorders

Review

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Autism is a neurodevelopmental syndrome that is defined by deficits in social reciprocity and communication, and by unusual restricted, repetitive behaviors (American Psychiatric Association, 2000). Autism is a disorder that usually begins in infancy, at the latest, in the first three years of life. Parents often first become concerned because their child is not using words to communicate, even though he or she recites passages from videotapes or says the alphabet. Though social deficits may not be immediately obvious in early years, they become gradually more evident as a child becomes more mobile and as other children become more socially sophisticated. Young children with autism often do not seek out others when they are happy, show or point to objects of interest, or call their parents by name. In preschool years, repetitive behaviors, such as using peripheral vision to look at lines or wheels, or specific hand and finger movements, begin to develop.

Autism is a heterogeneous condition; no two children or adults with autism have exactly the same profile, but difficulties fall into core domains that are reliably measured and usually consistent across time, even though specific behaviors may change with development. A child who may spend a great deal of time spinning objects and watching them out of the corner of her eye at age four, may not show this behavior at all as a teenager, but may be fascinated by sunroofs or bald heads or World War I. A child whose primary method of communicating requests at age two is to lead his mother to whatever he wants, place her hand on it, or use her hand to gesture toward it, may learn to ask for what he wants quite clearly and persistently by the time he is three or four, but continues to show difficulty carrying out back and forth conversations and coordinating eye contact and gestures.

Because of its links to genetics and neural development and the severe abnormalities in social interaction by which it is defined, autism offers the opportunity for scientists to study the neurobiological origins of social communication skills basic to human behavior. For example, even as infants, typically developing children are more adept at catching the eye of other people, coordinating vocalizations with their intentions, and communicating all but the most extreme emotions with facial expressions than are much older children or adults with autism. Autism is a disorder of contrasts between spared abilities and deficits in areas of social-communicative development that we take for granted: a child with autism who can recite the alphabet and recognize numbers may not turn to his name or follow a pointing gesture. As adults, individuals with autism have a range of outcomes from complete dependence to rare examples of successful employment. However, they almost never marry and only rarely form ordinary, reciprocal friendships. The possibility of identifying links between the acquisition (or failure of acquisition) of basic social behaviors and neurobiology has, in part, fostered the recent surge of interest in the neuroscience of autism.

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Issues in Diagnosis and Defining the Phenotype

Over the last 20 years, the conceptualization of a spectrum of autism-related disorders, including Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), which all include qualitative deficits in social behavior and communication, has been supported by longitudinal, epidemiological, and family studies (see Filipek et al., 2000 for a general review). However, these disorders vary in pervasiveness, severity, and onset. The umbrella category is termed Pervasive Developmental Disorder in the most common diagnostic systems (American Psychiatric Association, 2000; World Health Organization, 1992). Rett's syndrome has been included in the category of autism spectrum disorders within psychiatric systems because of the overlap in symptoms in toddlers and preschool children but, because of its different course (e.g., loss of purposeful hand use) and neurological characteristics (e.g., deceleration in head circumference), is a more differentiable group than the other syndromes and so generally studied as a distinct disorder. Clear distinctions among the other disorders within the autism spectrum, as listed on Table 1, are possible according to the degree of accompanying language deficit or general cognitive delay (American Psychiatric Association, 1994) or according to the severity of social or behavioral symptoms (Lord et al., 2000). Asperger's disorder involves the presence of autistic social deficits and repetitive, circumscribed interests in individuals who are verbally fluent. It has been of interest to scientists because of the contrast, as discussed earlier, between relatively intact and often verbose qualities of language and limited behaviors. Its prevalence is in dispute because, in controlled studies, it has been difficult to reliably differentiate Asperger's syndrome from autism without mental retardation or language delay, except by neuropsychological profile (which may be tautological).

On the other hand, the appeal of the different categorizations is in part because there is such a range of abilities and patterns of deficits within the autism spectrum that the possibility of finding subcategories related to

Table 1. DSM-IV/ICD-10 Diagnostic Criteria for Autism Spectrum Disorder

	Autistic Disorder	Rett's Disorder	Childhood Disintegrative Disorder	Asperger's Disorder	PDD-NOS
Age of Onset	Delays or abnormal functioning in social interaction, language, or play by age 3.	Apparently normal prenatal development; apparently normal motor development for first 5 months; deceleration of head growth between ages 5 and 48 months.	Apparently normal development for at least the first 2 years of birth; clinically significant loss of previously acquired skills before age 10.	No clinically significant delay in language, cognitive development, or development of age appropriate self-help skills, adaptive behavior, and environment in childhood.	This category is to be used in cases of pervasive impairment in social interaction and communication with presence of stereotyped behaviors of interests when criteria are not met for a specific disorder.
Social Interaction	Qualitative impairment in social interaction, as manifested by at least two of the following: a) marked impairment in the use of multiple nonverbal behaviors, i.e., eye-to-eye gaze; b) failure to develop peer relationships appropriate to developmental level; c) lack of spontaneous seeking to share enjoyment with other people; d) lack of social or emotional reciprocity.	Loss of social engagement early in the course (although often social interaction develops later).	Same as Autistic Disorder along with loss of social skills (previously acquired).	Same as Autistic Disorder.	
Communication	Qualitative impairments of communication as manifested by at least one of the following: a) delay in, or total lack of, the development of spoken language; b) marked impairment in initiating or sustaining a conversation with others, in individuals with adequate speech; c) stereotyped and repetitive use of language or idiosyncratic language; d) lack of varied, spontaneous make-believe or imitative play.	Severely impaired expressive and receptive language development and severe psychomotor retardation	Same as Autistic Disorder, along with loss of expressive or receptive language previously acquired.	No clinically significant delay in language.	
Behavior	Restricted, repetitive, and stereotyped patterns of behavior, as manifested by one of the following: a) preoccupation with one or more stereotyped or restricted patterns of interest; b) adherence to nonfunctional routines or rituals; c) stereotyped and repetitive motor mannerisms; d) persistent preoccupation with parts of objects.	Loss of previously acquired purposeful hand movements; appearance of poorly coordinated gait or trunk movements.	Same as Autistic Disorder, along with loss of bowel or bladder control, play, motor skills previously acquired.	Same as Autistic Disorder.	
Exclusions	Disturbance not better accounted for by Rett's or CDD.		Disturbance not better accounted for by another PDD or schizophrenia.	Criteria are not met for another PDD or Schizophrenia.	

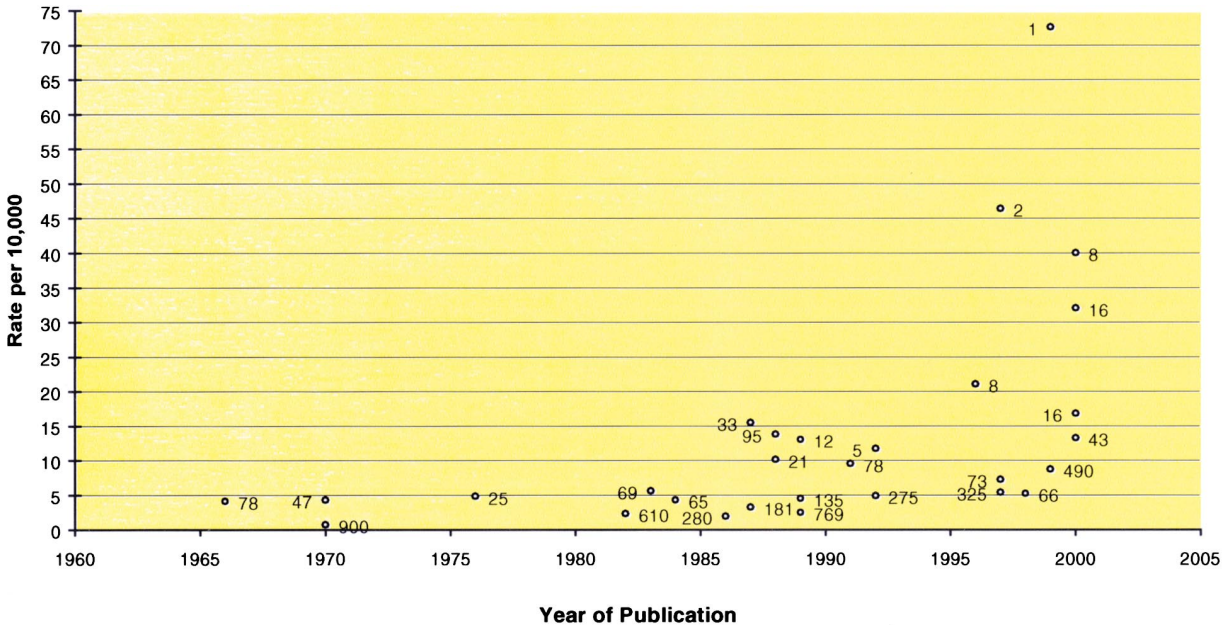

Figure 1. Autism Prevalence in 29 Studies

Numbers indicate thousands in each target population.

etiology or pathophysiology continues to be enticing. In addition, the range of services needed across the autism spectrum is very broad, particularly once children reach elementary school and into adulthood. For example, a child with high functioning autism or Asperger's syndrome may do well academically in a fifth grade program for children gifted in mathematics but need the support of an assistant teacher in order to benefit from social activities and help him as he begins to understand that he is different from other children. Another child the same age whose understanding of language and speech is limited to single words and a few familiar phrases may need continuing speech therapy on vocabulary as well as benefit from the use of a picture system that allows her to understand the schedule for the day and communicate how she would like to spend her free time at school and at home. The value of the spectrum diagnoses is to recognize that both of these children have significant deficits that share similarities as well as differences.

In the last 10 years, standardized measures of autism-related deficits have been developed that reliably measure history and present status, with relative independence from cooccurring language delays or mental retardation. Standard diagnoses of autistic disorder, Childhood Disintegrative Disorder, and PDD-NOS can be made across a wide range of individuals of different ages, language levels, and nonverbal abilities, including young children. Severity of social and communication deficits can be reliably quantified (see Filipek et al., 2000; Lord et al., 2000). Experiments based on developmental cognitive theories have identified increasingly specific points in maturation when "pivotal" behaviors, such as imitation, joint attention, and orienting to social stimuli, fail to develop normally in autism (Osterling and Dawson, 1994). In addition, autism affects not only social behavior and language but also many other aspects of functioning, including sensory responsiveness, play, and motor activity. Approximately 30% of autistic patients also have an associated seizure disorder.

As shown in Figure 1, adapted from Fombonne (1999), epidemiological studies indicate an increasing prevalence for autism spectrum disorders in the last 15 years. Much of the higher rates may be accounted for by more complete ascertainment and the expansion of diagnostic frameworks to include milder forms of the disorder (Fombonne, 1999). However, it is interesting to note that the highest estimates of prevalence have all occurred in the last 5 years, though in small samples in studies where diagnoses were not always based on standard clinical procedures. These findings and the increases in the numbers of children with autism spectrum disorder referred to school systems (see Baird et al., 2000) and state programs have sparked the interest of many advocacy and scientific groups. The question of rising prevalence is particularly difficult to study because measures and diagnostic systems to establish base rates have changed greatly in the last 10 years, and, though available now, are expensive and time consuming (e.g., require a substantial parent interview and structured observation) if the milder forms of autism spectrum disorder are to be identified.

Many, but not all, individuals with autism, have mental retardation and almost all individuals with autism have a history of language delay. However, there are autism spectrum disorders (e.g., Asperger's disorder) in which neither language delay nor mental retardation is present. Families with children with moderate or mild mental retardation or normal intelligence with autism are no more likely to have children with mental retardation without autism than other families. Thus, the mental retardation appears to be a part, but not a necessary part, of autistic

disorders. There is some suggestion that lesser variants of communication difficulties may be familial, not necessarily cooccurring with other features of autism (Folstein et al., 1999). Language delay and milder communication difficulties overlap with many other disorders, however. The relationship between language impairment and autism is an important area of study that requires careful selection of measures and comparison groups because of the variability within normal development, frequent associations with other disorders, and the need to measure the presence of specific social deficits across a range of language levels (e.g., measuring social skills is different in a nonverbal than verbal child). Another approach has been based on the significant minority of individuals with autism who have "islets of ability," usually in skills that require attention to detail, memory, or computations (e.g., such as calendrical calculating or perfect pitch—see Prior and Ozonoff, 1998). Baron-Cohen et al. (1995) have followed up on this notion to suggest that the incidence of autism may be higher in families where a parent has selected a field of interest where imagination and social skills are less emphasized and attention to detail and focus are particularly important, such as engineering or basic science. The question of what are the broader phenotypes of autism and do they extend into differences within the normal population is very complex and just beginning to be studied systematically.

Genetics of Autism

The genetics of autism is an area that has stimulated much recent research (see Cook, 1998, 2000 for recent reviews). Possibly the most significant genetic finding relevant to autism is the recent identification of the gene responsible for Rett's syndrome (Amir et al., 1999). Rett's syndrome is a neurodevelopmental disorder that is associated with mental retardation, loss of communication skills, and autistic features that vary in prominence at different developmental stages. It has been, somewhat controversially, placed within the diagnostic category, pervasive developmental disorders, of which autism is the exemplar. Rett's syndrome is caused by mutations in the methyl-CpG binding protein 2 gene (*MECP2*). Decreased expression of *MECP2* leads to the failure to suppress expression of gene(s) regulated by methylation. When the pathophysiology of *MECP2* mutations is further elucidated, it is likely to add to an understanding of autistic disorder.

Autism spectrum disorders are also seen in a substantial minority of patients with full mutations of the Fragile X (FRAXA) gene *FMR1*. The reverse is not the case, since full *FMR1* mutations are seen in less than 1% of recent samples of children with autism. More importantly, analysis of this single gene disorder will contribute to an understanding of the mechanisms by which reduced *FMR1* expression leads to mental retardation and to social-communicative symptoms that overlap with those seen in autistic disorders.

Autism is a paradigmatic complex genetic disorder, similar to diabetes, asthma, schizophrenia, Alzheimer's disorder, and many others. The sibling recurrence risk is approximately 4.5%, relative to a population incidence and estimated prevalence of approximately 0.1%–0.5%. This relative risk to siblings (λ_s) of 9–45 is one of the highest for a complex genetic disorder and is higher than the other disorders listed above. The most compelling evidence for high heritability is the greater than 50% concordance rate for monozygotic twins relative to an $\sim$3% concordance for dizygotic twins. This also suggests multiplicative genetic effects in which more than one and probably more than 2 genes contribute in concert to the high risk for monozygotic twins.

The current focus in molecular genetics of autism is on the identification of molecular genetic variation that contributes to autism susceptibility. Candidate gene findings of interest include a family-based association and linkage finding between the serotonin transporter promoter gene insertion/deletion polymorphism and autistic disorder. Of family-based, controlled studies, one showed preferential transmission of the short arm of the serotonin transporter promoter gene. Two showed transmission of the long arm and two were not significant. Genetic or clinical heterogeneity or multiple tests of candidate genes leading to false positives may have led to this inconsistency. Another candidate gene finding has been one between a microsatellite near the alternative promoters and first 3 exons of the $GABA_A$ β 3 subunit gene (*GABRB3*), but this has also not been found in all samples.

The chromosomal disorder most frequently found (0%–3%) in recent large samples of autism has been the finding of a maternal duplication of 15q11-q13. This is the same region in which absent maternal gene expression (or mutation) of ubiquitin binding enzyme 3A (*UBE3A*) leads to Angelman syndrome and in which the absence of paternal chromosomal gene expression leads to Prader-Willi syndrome, two other developmental disorders associated with mental retardation, but that are associated with quite different phenotypes than autistic disorder. Although there may be a convergence of the linkage disequilibrium findings for *GABRB3* and the 15q11-q13 duplications, it is also possible that the duplication of 15q11-q13 has distant effects, such as the overexpression of *UBE3A*, leading to excessive degradation of one or more of its targets.

Several genome-wide screens have been published in autism in the past 3 years (reviewed in Cook, 2000) and more are in progress. Much effort is now focused on confirming the strongest finding from the first published study, i.e., a linkage in a relatively large region (7q32-35). Several other regions of interest have been identified across different genome scans, including 2q, 16p, 19p (e.g., see http://www.agre.org/bnews/scan.cfm).

Neurobiology of Autism

A fundamental goal of neurobiological approaches to the study of autism is the definition of brain regions that are most severely affected. Once affected brain regions are identified and the types of alterations (structural versus neurochemical; failure of development versus degeneration) are better understood, strategies can be developed for prevention, early diagnosis, and treatment. The neurobiology of autism has been hampered, in part, by the heterogeneity inherent in the autism spectrum disorders. It is not currently clear whether autism is a syndrome that varies in severity but nonetheless has

a common neural basis or whether the autism spectrum disorders have multiple etiologies and affect various brain systems that nonetheless lead to the core deficits of abnormal social behavior, impaired communication, and stereotypical behavior. Clearly, in this as in every other area of autism research, future progress will depend on better categorization of distinctive subsets of autistic individuals using biochemical, genetic, neuroimaging, behavioral, and other diagnostic tools.

One approach to the neurobiology of autism, the neuropathological approach, employs both postmortem analysis and noninvasive imaging techniques to determine the brain regions involved in autism. A second approach attempts to understand the normal neural substrates of functions, such as social cognition, that are profoundly impaired in autistic disorders. It is a reasonable expectation that one or more components of this system might be altered in autism. Thus, the neurobiology of normal social behavior can potentially narrow the scope of suspect brain regions. A third, but currently more poorly developed approach, is the development of animal models. This effort has been hobbled by a lack of knowledge concerning the etiology(ies) of autism and a paucity of data, which is also highly variable, on the characteristic neuropathology of autism, i.e., it is not quite clear what a successful model of autism would look like.

Neuropathology

Although autopsy studies of autism were begun in the early 1980s, formal reports have only involved about 30 brains. There are a number of reports that the brains of autistic individuals are larger than normal. Bailey et al. (1998), for example, found that four of six postmortem brains that they examined, from individuals ranging in age from 4 to 24 years at time of death, were megalencephalic. Regional neuropathological studies have pointed to possible alterations in the brainstem, cerebellum, and in a set of "limbic" structures, including the hippocampal formation, amygdala, septal nuclei, and anterior cingulate cortex. Cells in various portions of the hippocampal formation, in the medial nuclei of the amygdala, the medial septal nucleus, the mammillary nuclei, and the cortex of the anterior cingulate gyrus tend to be smaller and more densely packed than in normal brains (Kemper and Bauman, 1998). Neurons in the hippocampus of autistic individuals also have reduced complexity of dendritic arbors. Some pathology seems to be age dependent. In the basal forebrain nucleus of the vertical limb of the diagonal band of Broca, for example, neurons were unusually large and numerous but otherwise normal looking in brains of autistic children less than 12 years old but were small and reduced in number in brains of autistic adults older than 18 years. The Bailey et al. (1998) study confirmed qualitative impressions that cell density was higher in the hippocampus of autistic individuals but morphometric analyses did not demonstrate significant differences. They also noted abnormalities in the cytoarchitectonic organization and neuronal density of the superior frontal cortex and superior temporal gyrus of some of their cases but no quantitative differences were found.

Cerebellar abnormality has been a common finding. Ritvo et al. (1986) noted that there was a loss of Purkinje cells in the brains of four subjects with autism. Kemper and Bauman have generally confirmed the loss of cerebellar Purkinje cells and reported changes in neurons of the deep cerebellar nuclei. Bailey et al. (1998) also observed loss of Purkinje cells but no apparent changes in the number of granule cells or alterations of deep cerebellar nuclei. It is important to note that the loss of Purkinje cells is also a common correlate of seizure disorders (Dam, 1992), and it is essential to determine whether loss of this neuron class also occurs in autistic subjects who are seizure free.

Rodier et al. (1996) found near complete absence of the facial nucleus and superior olive in one postmortem case. Bailey et al. (1998) also found brainstem abnormalities of the superior and inferior olives; however, the organization of the facial nucleus was not evaluated. Kemper and Bauman reported alterations in the portion of the inferior olive that projects to the part of the cerebellar cortex with the most profound loss of Purkinje cells.

The lack of a coherent description of the neuropathology of autism is undoubtedly due, in part, to the relatively small number of brains that have been analyzed and to the use of qualitative methods of assessment. Future progress, both in neuropathological assessment of the autistic brain and in studies of the molecular biology of autism, will require the acquisition of high quality post mortem tissue from well-characterized donors.

Structural Magnetic Resonance Imaging Findings

Given the relatively subtle and variable neuropathological changes that have been described in the autistic brain, it is not surprising that structural magnetic resonance imaging studies have not found consistent changes. Courchesne et al. (1988) reported selective hypotrophy of vermal lobules VI and VII in the cerebellum of autistic subjects. This has proven to be a controversial finding and others have failed to consistently replicate it. One explanation may be that not all subsets of the autistic spectrum demonstrate cerebellar hypoplasia. Holttum et al. (1992) found, for example, that cerebellar hypoplasia does not appear to be associated with high-functioning autism. Saitoh and Courchesne (1998) later found that there were two subgroups of autistic subjects that were characterized either by hypoplasia or hyperplasia of lobules VI and VII. Thus, depending on the composition of a patient population, one might expect to see hypoplasia, hyperplasia, or no change.

Abell et al. (1999) used a voxel-based whole brain analysis and identified gray matter differences in the amygdala and associated brain regions. Decreases of gray matter were found in the right paracingulate sulcus and the left inferior frontal gyrus, whereas increases were found in the amygdaloid complex (particularly the periamygdaloid cortex) the middle temporal and inferior temporal gyrus, as well as in regions of the cerebellum. It is not clear how these changes in MR signal characteristics relate to the increased density of smaller neurons seen in many of these same areas. Aylward et al. (1999) found that the volumes of both the amygdala and the hippocampal formation were reduced in the autistic brain, though neither Piven et al. (1998) nor Saitoh et al.

(1995) observed changes in the hippocampus. Consistent with the neuropathological findings of Kemper and Bauman, Haznedar et al. (1997) observed decreased volume and decreased PET activity in the anterior cingulate gyrus of autistic subjects. Finally, there have been no neuropathological findings in the basal ganglia of autistic patients. However, Sears et al. (1999), using structural MRI, observed an increased volume of the caudate nuclei in autistic subjects that was proportional to compulsions and rituals.

Neurobiology of Social Behavior

Regardless of whether an individual with an autism spectrum disorder is mentally retarded or not and whether the individual has language impairment or obvious stereotypical behaviors, all persons with autism spectrum disorders have some disturbance of normal social behavior. These deficits range from subtle abnormalities in social reciprocity, particularly with peers, to much more obvious difficulties in the use of eye contact, facial expression, and social motivation. A growing body of literature indicates that important aspects of social cognition, such as the salience or interpretation of facial expressions or the appreciation of angle of gaze, are markedly impaired in autistic subjects (Baron-Cohen et al., 2000). Thus, an understanding of the brain systems responsible for social cognition and for interpretation of the social aspects of facial expression might be predictive of regions of brain dysfunction in autism.

Evidence from both human and animal studies indicates that certain brain regions are preferentially involved in social behavior. In the macaque monkey, these would include the amygdala, orbitofrontal cortex, superior temporal gyrus, and temporal polar cortex. Damage to any of these regions in macaque monkeys produces a profound alteration of social behavior. Cortical areas, such as the anterior cingulate gyrus, have also been implicated in the production of species-specific vocalizations. Yet, other cortical regions, such as the inferior temporal gyrus in monkeys and the fusiform gyrus in humans, appear to be preferentially involved in the perception of faces. Neurons ("face cells") that are highly and selectively responsive to the image of faces have been found in the inferior temporal gyrus of macaque monkeys (Perrett et al., 1982). Neurons sensitive to the angle of gaze have been found in the cortex of the superior temporal sulcus (Perrett et al., 1985). Neurons that are attuned to particular facial expressions have also been found in the inferior and superior temporal lobes of macaque monkeys (Hasselmo et al., 1989). Interestingly, cortical areas responsive to faces, facial expressions, and to angle of gaze send direct projections to the primate amygdala (Stefanacci and Amaral, 2000). These functional and neuroanatomical facts have raised the prospect that the amygdala may be important for components of social cognition such as the attention to and interpretation of facial expressions. If this is the case, the amygdala is a prime candidate for dysfunction in autism.

A rare human disorder called Urbach-Wiethe syndrome produces cystic calcifications of the medial temporal lobe. In patient SM, these space-occupying lesions mainly involve the amygdala bilaterally and she is markedly impaired in her ability to judge facial expressions of fear and anger (Adolphs et al., 1995). Even more germane to the pathology of autism, SM is unable to make an accurate judgement of the trustworthiness of an individual from photographic images. Functional imaging studies have demonstrated activation of the amygdala in normal subjects asked to make judgements of facial expressions. Very recently, Baron-Cohen and colleagues (1999) carried out a functional magnetic resonance imaging experiment using a test of judging from the expressions of another person's eyes what that other person might be thinking or feeling. In normal subjects, this test resulted in activation in the superior temporal gyrus and the amygdala with additional activations in the frontal cortex. In the autistic population that they studied, the task produced activations in the temporal lobe and in the frontal cortex but not in the amygdala. These interesting observations will need to be confirmed and extended but raise the prospect that pathology of some sort in the amygdala may play an important role in the defects of social cognition observed in autism. Schultz and colleagues (Schultz et al., 2000) compared activation in the inferior temporal gyri (ITG) during face and object processing in individuals with autism or Asperger's disorder and those with typical development. Individuals with autism spectrum disorders used ITG significantly more during face processing than did normal controls, though the side of the effect varied across an initial and a replication group. Thus, in this study, individuals with autism used strategies typically used in nonface object perception by normal adults in order to discriminate faces. More work on relatively young, homogeneous samples, which balance scientific rigor with ethical restraints, are much needed (Rumsey and Ernst, 2000).

Animal Models

The most successful animal model of autism produced to date involves the bilateral removal of the medial temporal lobe of young macaque monkeys (Bachevalier, 1996). These animals show a variety of socioemotional changes including social isolation and demonstrate some other facets of autistic symptomatology such as stereotypical behaviors. Clearly, the production of large medial temporal lobe lesions does not closely mimic the pathology observed in the autistic brain. It would be interesting if more subtle and more focal dysregulation could be produced in the developing nonhuman primate brain that replicated the autistic behavioral pathology.

Other investigators have attempted to model the neuropathology observed in the brain stem using various teratogens. This work has been motivated by the finding that certain children exposed prenatally to thalidomide developed some symptoms of autism. Rodier and colleagues (1996) have used maternal treatment with valproic acid in rats in an attempt to produce pathology in cranial nerve nuclei (reviewed in Rodier, 2000). The alterations that Rodier and colleagues observed in their patient with autism involved mainly the facial nucleus and the superior olive. In her valproate studies, Rodier observed changes in motor nuclei of V and XII with later treatments affecting the VIth and IIIrd cranial nerve nuclei. None of her treatments affected the facial nu-

cleus (unlike in the postmortem autistic brain). Morever, Rodier et al. (1996) observed that there were no changes of any other brain regions such as the cerebellum, hippocampus, or amygdala. Therefore, even based on the minimal neuropathology available, the valproic acid model would not appear to have much verisimilitude to human autism.

Interventions, Families, and Needs for the Future

Given the limited information available on the etiology(ies) and biology of autism, therapies have generally focused on educational and behavioral interventions. There are increasing efforts to evaluate psychoactive drugs for clinical benefit in autism. For example, a large multisite study is in progress (McDougle et al., 2000) of the effects of risperidone (a serotonin 5HT2A/dopamine D2 receptor blocker), which showed some benefit in a single double-blind placebo-controlled trial in terms of reducing maladaptive behaviors without demonstration of independent effects on core social and communication deficits.

Currently, intensive, structured education forms the core of most treatment approaches, supplemented by positively oriented behavior management, family support, and an emphasis on functional communication. Children and adults with autism can clearly benefit from direct teaching and exposure to developmentally appropriate experiences. Controversy remains, however, as to whether it is possible to alter the trajectory of the development of a child with autism or whether early interventions primarily accelerate development in children who would make good progress in response to many treatments or reduce secondary effects of social isolation and lack of engagement. These issues have been linked, so far without data, to larger questions of neuroplasticity and the degree to which social engagement contributes to basic cognitive functions (Mundy and Neal, 2000).

The variation in outcomes in autism spectrum disorders, from severe behavioral disturbance and profound mental retardation, to uncommon cases of independent, age appropriate functioning, and the limited success of current therapies in completely diminishing the symptoms of autism, has resulted in some parents becoming increasingly experimental in approaches to their child's treatment. This makes parents vulnerable to new claims of remarkable improvements, particularly in response to highly publicized treatments, such as facilitated communication, auditory training, dietary manipulations, and, recently, secretin (Volkmar, 1999). In the last case, a serendipitous finding of behavioral improvement following the administration of secretin during endoscopy (Horvath et al., 1998) led to widespread demand for this "treatment" by parents. Since then, several double blind, placebo-controlled clinical trials of secretin have found it to have no positive effect on autism (e.g., Sandler et al., 1999). Other clinicians and parents have promulgated the practice of controlling the diet of children with autism. Most prominently, gluten-free and casein-free diets have been purported to benefit young children with autism, particularly. Recommendations for such dietary restrictions are based on extremely limited scientific data (Lucarelli et al., 1995), though advocates of such approaches counter that there is little evidence (Sponheim, 1991) against them.

Another issue that has arisen recently is the proposal that at least some cases of autism in which children have had a few words and other social-communicative behaviors that disappear in the second year of life may be linked to vaccinations. This pattern of loss of words often accompanied by increasingly obvious social deficits is described by parents as occurring in about one-fifth of children with autism. The particular vaccinations proposed as causal have varied, but currently the greatest focus has been on combination vaccines for measles, mumps, and rubella (Kawahima et al., 2000; Wakefield et al., 2000). This suggestion, based on research carried out primarily by Wakefield and colleagues, has been extraordinarily controversial. A number of epidemiological studies from countries with comprehensive health registers have appeared not to support a link between MMR vaccines and autism (Taylor et al., 1999; Afzal et al., 2000). Here again, there is a chasm between the visible increase in prevalence of autism as indicated by the need for services, and empirical evidence for the gradual broadening of criteria and improvements in identification, which is felt by some not to be sufficient to account for the increases. It is not surprising that parents and some clinicians and researchers have attempted to account for this gap, with alternative theories.

Parents' societies have traditionally been very important to the field of autism, from the founding of the first autism societies in the US and UK many years ago, to the current research support and advocacy provided by a number of parent-founded, -led, and -supported organizations. These organizations have already begun to be influential in terms of research, especially in funding new investigators and attracting eminent scientists from other fields into studying the disorder. The parents' organizations also have the potential to be extremely helpful in dissemination of scientific information, particularly on the Internet, which, with the hundreds of sources available, provides a tremendous but sometimes overwhelming amount of information.

Sometimes claims for extraordinary outcomes are unwittingly promulgated by scientists unfamiliar with the range of behaviors and developmental course seen in autism spectrum disorders and impatient with standard clinical research procedures such as random assignment, double-blinding, and case-controls. On the other hand, new ideas from diverse perspectives on treatment, prevention, and understanding of the pathophysiology of autism are urgently needed. One of the foremost goals for the next decade will be greater communication between basic scientists, clinical researchers, parents, and persons with autism spectrum disorders so that knowledge from neuroscience and other areas of biology can be more readily applied to autism in ways that yield scientifically valid and effective results.

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