CURRENT DIRECTIONS IN RESEARCH ON AUTISM

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One of the most active areas of current research in the field of developmental disorders is autism. Since the NIH State of the Science conference, held in 1995 (Bristol et al. [1996]. Autism Dev. Disorders 26:121–154), funding opportunities for comprehensive research programs addressing genetic, neurobiological, and behavioral aspects of this complex disorder have grown exponentially. Although we are far from having a complete understanding of the causes and deficits that define autism, significant progress has been made over the past few years. In this review, we summarize recent developments across a number of different areas of research in the field of autism, including diagnosis, defining the phenotypic features in individuals with autism; genetic bases; and neurobiological deficits.

DIAGNOSIS OF AUTISM

Defining Autism

In concept, the diagnosis of autism has not changed since it was first formulated by Leo Kanner in 1943: abnormal development of social reciprocity, abnormal development of language, especially as it is used for communicating with other persons, and desire for sameness, as seen in repetitive rituals or intense circumscribed interests [Kanner, 1943; APA, 1994]. There have, however, been changes in how these concepts have been interpreted, and these changes have resulted in larger numbers of individuals being diagnosed with autism.

One important development in diagnosis has been the nearly universal acceptance of and use of a single set of diagnostic instruments for documenting cases for research: the Autism Diagnostic Interview (ADI; LeCouteur et al. [1989]) and the Autism Diagnostic Observation Schedule (ADOS; DiLavore et al. [1995]). The introduction of these instruments has fostered collaborative studies since it is now possible to coordinate across studies and to combine samples of people with autism, all diagnosed in a uniform and reliable way, collected by different investigators at different sites.

Beginning in the 1980s, Rutter and colleagues began to develop a structured diagnostic interview for autism, the ADI that is now the standard diagnostic instrument for research of all types in autism. It has been shown to be reliable, and, after validating the ADI against clinically diagnosed children with mental retardation but without autism, it was revised [Lord et al., 1994]. The ADI-Revised version (ADI-R) employs an algorithm score that has good discriminant validity for autism and mental retardation [Lord et al., 1997]. On the other hand, it should be noted that the ADI-R is less good at discriminating among different forms of Pervasive Developmental Disorders (PDD), including Asperger syndrome and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

The companion instrument to the ADI-R is a structured, direct interaction with the child that is mainly a press for various aspects of social and communicative interaction, called the Autism Diagnostic Observation Schedule-Generic (ADOS-G). In the current edition, one of four modules of the ADOS-G is used, depending on the person’s age and verbal ability [Lord et al., 2000]. Although the presence of repetitive behaviors and obsessive interests is scored during the administration of the ADOS-G, these items are not included in the algorithm used to make a categorical judgment about the diagnosis of autism.

Spectrum of Autism Disorders

Autism is now popularly thought of as a spectrum of conditions united by difficulties in social interaction, pragmatic language, and repetitive behaviors or obsessive interests. The spectrum ranges from children who meet behavioral criteria for autism but have known medical disorders (e.g., tuberous sclerosis), to classic autism (Kanner-type), to cases that nearly meet criteria (PDD-NOS), to children who have normal development of structural language but difficulties with social communication and rigid, stereotyped interests and behaviors (Asperger syndrome).

This concept of a “spectrum of autism” has been partially validated. The word spectrum has usually been used in psychiatry to suggest that all the components are conceptually and etiologically related but that they differ in severity. Family studies suggest that several varieties of the spectrum can be found in the same families [Folstein and Santangelo, 2000]. Very limited autopsy studies suggest a basic similarity in microscopic pathology in cases with a variety of language and intellectual capacities [Kemper and Bauman, 1998]. Lastly, functional brain-imaging studies (which have mainly studied more intellectually able children because they can better cooperate with the studies) do not suggest anatomic differences between adults with autism.
and those who meet criteria for Asperger syndrome as currently defined [e.g., Happé et al., 1996; Schultz et al., 2000]. Thus evidence is accumulating that the concept of a spectrum in autism is a valid one.

There is an ongoing debate regarding the distinction between autism, especially in high functioning individuals, and Asperger syndrome [e.g., Eisenmajer et al., 1998; Szatmari, 1998]. The diagnostic concept Asperger syndrome (AS) was concurrently introduced into DSM-IV and ICD-10 on the basis of similar definitions. The term AS is, however, still used in somewhat different ways by clinicians to refer to high-functioning individuals with autism and adults with autism or a sub-threshold form of PDD-NOS [Volkmar et al., 2000]. In other disciplines it appears that a similar condition to AS is referred to by different labels including semantic–pragmatic disorder [Bishop, 1989], and right-hemisphere or non-verbal learning disability [Rourke, 1989]. These differences in the use of the term AS and differences across disciplines in taxonomy have led to complications in how to interpret current research on the validity of the diagnosis.

According to Volkmar et al. [2000], AS may be distinguished from autism and PDD-NOS on the basis of higher verbal IQs, greater social deficit, higher rates of the disorder in first-degree relatives, and different patterns of co-morbidity, especially higher rates of depression. However, Manjiviona and Prior [1999] did not find differences in the neuropsychological profiles of children with AS and autism, but they did confirm that children with AS had higher verbal abilities as measured on IQ tests. Similarly, Ozonoff and colleagues [2000] found that children with AS showed the same fundamental symptoms as children with high-functioning autism, only in less severe forms, especially during the early years of development. Future research will need to continue to address the differences between subtypes of autism that fall on the spectrum of disorder, especially between AS and high-functioning autism.

Prevalence Rates of Autism

In recent years, due to changes in the operationalization of the diagnostic criteria, improvements in early detection, and the concept of a spectrum, it appears that the prevalence of autism is increasing. This apparent change of prevalence has sparked concern, particularly among families with affected children, to look for new causes, such as vaccination with measles, mumps, and rubella (MMR) vaccine and living near industrially polluted areas. The latter has not been carefully studied, and there is no scientific evidence for the former [Taylor et al., 1999]. There was no surge in prevalence that coincided with the use of either mumps or MMR vaccine. It is well known that some small proportion of autism begins or at least becomes much worse at around 18–20 months of age, when most children receive the MMR vaccine, although the reason for this pattern of "regression" is not known.

One explanation for the apparent increase in prevalence of autism takes account of the secular trends in diagnosis. The clearest example is provided by the work of Gillberg et al. [1991]. He and his colleagues carried out three surveys of individuals with autism and adults with autism or a sub-threshold form of PDD-NOS in the same city in Sweden over the course of a decade. In the first survey conducted in 1980, the prevalence was 4/10,000, and the prevalence rose in each subsequent survey to 11.6/10,000 in 1988. The prevalence of "classic autism" was the same in all three surveys. However, in the later surveys, the prevalence of non-clasical autism increased at both the low and high ends of the IQ range.

Other factors contributing to the apparent increase in prevalence of autism is the popularization of the idea of the "spectrum." This has resulted in many socially peculiar children, who do not meet current or past criteria for autism, being considered as in the "autism spectrum" [cf. Gillberg and Wing, 1999]. Furthermore, considerable effort has been made to teach pediatricians and other clinicians who see very young children to identify abnormalities of language and social interaction, so that many children who were undiagnosed are now being identified [see Filipek et al., 1999]. In a recent review of epidemiological surveys of autism published over a 30-year period, Fombonne [1999] found that prevalence rates of autism significantly increased with publication year, which he attributed to changes in case definition and improved recognition of the disorder in clinical practice. Based on his review of recent studies, Fombonne proposed that a minimum estimate for all forms of PDD was 18.7 per 10,000.

CORE PSYCHOLOGICAL FEATURES OF AUTISM

According to Volkmar et al. [2000], AS may be distinguished from autism and PDD-NOS on the basis of higher verbal IQs, greater social deficit, higher rates of the disorder in first-degree relatives, and different patterns of co-morbidity, especially higher rates of depression.

Central Coherence

Interestingly, the remarkable skill demonstrated by individuals with autism on Block Design has been argued to derive from an abnormality in information processing hypothesized as weak central coherence [Frith and Happé, 1994]. This hypothesis postulates a failure of holistic processing in autism and a subsequent bias toward local, part-oriented processing. Thus, on Block Design, it is argued that individuals with autism do not succumb to the overall form or gestalt of the design they are asked to reconstruct, and as a result find it easier to see their component parts [Shah and Frith, 1993].
Other studies supporting the weak central coherence hypothesis (see Happé [2000] for reviews) have found that individuals with autism are less susceptible to visual illusions [Happé, 1996]; they benefit less from canonical die patterns in dot counting [Jarrold and Russell, 1997]; they appear to be especially skilled at identifying “hidden” parts in the Embedded Figures Test [Shah and Frith, 1983; Jolliffe and Baron-Cohen, 1997; but see also Brian and Bryson, 1996]; and they fail to use linguistic context to disambiguate homographs when reading sentences aloud [Frith and Snowling, 1983; Happé, 1997]. Yet, a number of recent studies [Mottron et al., 1999; Plaisted et al., 1999a, 1999b] have provided evidence of intact global processing abilities in autism that would appear to contradict the weak central coherence hypothesis. Moreover, there is as yet no evidence that the wide-ranging processing abnormalities attributed to weak central coherence actually co-occur within individuals, as would be expected if they arose from a single cognitive dysfunction. Thus, although the idea of weak central coherence may capture an essential quality of cognition in autism, its actual neuropsychological underpinnings remain to be elucidated and are likely to include multiple, interacting abnormalities and deficits in attention [e.g., Wainwright-Sharp and Bryson, 1993], perception [e.g., Plaisted, 2000], and higher-level reasoning abilities [e.g., Minshew et al., 1997].

Executive Functions
An alternative to the weak central coherence theory of autism has been the executive dysfunction hypothesis [Pennington and Ozonoff, 1996; Russell, 1997], which focuses less on abnormalities in information processing per se than on deficits in executive control over information processing and the regulation of behavior. Executive functions are typically called upon in non-routinized, problem-solving tasks and include mental operations such as planning, working memory, maintenance and shifting of attention and mental set, and inhibition of automatic or prepotent responses. Deficits in executive function could therefore potentially explain the repetitive and rigid behaviors of autistic individuals and their impaired ability to engage in reciprocal social interactions, which require flexible, on-line evaluation of and selection of appropriate responses to a continuous stream of subtle, multidimensional information [Bennetto et al., 1996].

Initial findings indicative of executive dysfunction in autism (see Pennington and Ozonoff, [1996] for a review) were based largely on omnibus clinical measures, such as the Wisconsin Card Sorting Test. Such measures, however, do not allow identification of the specific executive control functions that were impaired in autism and confound executive and non-executive cognitive skills. More recent research has adopted information processing paradigms to see if a specific pattern of executive deficit might be linked to autism and its core symptoms (see Ozonoff, 1997). For example, Ozonoff and colleagues [Ozonoff and Strayer, 1997; Ozonoff et al., 1994] found that children with autism were able to inhibit a simple response (e.g., pressing a button for circles but not for squares) but had difficulty when required to shift from one response set to another (e.g., pressing a button for squares instead of circles).

Thus, the findings from young children with autism suggest that, although executive function deficits may be characteristic of autism, they do not drive the core social and communicative abnormalities in autism and may be a more general correlate of developmental neuropathology and/or mental retardation.

Social Cognition
The focus of research on social cognitive impairment in autism has been dominated by the theory of mind hypothesis, first proposed by Baron-Cohen et al. [1985]. In this view individuals with autism have primary deficits in understanding that people’s behavior can be interpreted on the basis of their mental states such as desire, belief, and knowledge [Baron-Cohen et al., 1993]. Research on theory of mind abilities in both children and adults with autism continues to flourish [Baron-Cohen et al., 2000], though more recently, criticisms have begun to surface regarding its explana-
tory power. For example, some have questioned whether theory of mind impairment is universal and specific to autism [Yirmiya et al., 1998]. Nevertheless, its importance lies in its ability to provide a unified explanation for the social and communicative impairments that are among the core diagnostic characteristics of autism [e.g., Tager-Flusberg, 1999]. Individuals who fail to appreciate that people have “mental states” would clearly have trouble interacting with others and in understanding the essential nature of communicating for either social reasons or to exchange information.

The emphasis in the experimental literature on theory of mind has been on children’s performance in structured experimental tasks, such as the false-belief paradigm. These tasks tap children’s understanding that the mind is a representation of the world, not a direct copy. For example, when shown that a familiar container such as a milk carton contains paper clips, children who fail to appreciate the representational nature of mind will claim that another person who sees the milk carton will think that it contains paper clips, rather than milk. By the time typically developing children reach the age of four, they are able to correctly report their own and another person’s false belief about the contents of the carton (i.e., milk). However, children with autism continue to fail this task long after this point. Happé [1995] found that children with autism could not pass this task until their verbal mental age was at least eight years. Some recent criticisms of the theory of mind hypothesis may be related to the emphasis on these kinds of tasks. One concern is that some children with autism pass these tasks, despite their continuing social and communicative impairments. Second, performance on these tasks appears to be closely related to language ability [e.g., Tager-Flusberg and Sullivan, 1994; Sparrowohn and Howie, 1995; Tager-Flusberg, 1997], especially knowledge of complex syntax. This has led some researchers to suggest that problems with representational theory of mind tasks reflect limitations and impairments in the linguistic knowledge of children with autism [Tager-Flusberg, 2000]. Alternatively, failure on tasks tapping theory of mind has been interpreted as the result of deficits in executive functions. For example, Russell [1997] argues that theory of mind tasks entail action monitoring and self-regulation, which are also viewed as more primary impairments in autism. Furthermore, it is clear that symptoms of autism emerge long before children are able to pass false-belief tasks, suggesting that theory of mind must predate this stage of development if it is to be used as a viable explanation of the core social and communicative impairments [e.g., Klin and Volkmar, 1993; Klin et al., 2000].

In response to these criticisms, recent discussion of theory of mind impairments in autism focuses on a broader conception of this cognitive capacity. Taking a developmental perspective, theory of mind is now viewed as emerging in late infancy, with its development extending well beyond the preschool years [Tager-Flusberg, 2001]. The roots of understanding the intentional or mentalistic nature of human action lie in infants’ strong interest in people as evident in their attention to human faces and language, and their ability to respond to affective expressions within the first few months of life. Studies of early clinical markers of autism emphasize the signs in young toddlers of problems with eye contact, affect, orienting and responding to others and attention to language [e.g., Dawson et al., 1998b; Stone et al., 1999], all suggesting profound difficulties in relating to other people [Klin et al., 2000].

In addition to recognizing the early emergence of theory of mind capacities in infancy, research has begun to address theory of mind in older individuals, using paradigms that are more sensitive to deficits in the everyday use of mental state understanding. Language and Communication

Over the past two decades, most research on the language and communicative deficits in autism has focused on those aspects that are universal and specific to this disorder [Tager-Flusberg, 1996]. Beginning with Balthaxe [1977], studies explored the pragmatic deficits that are apparent in conversations and other discourse contexts, identifying those features that distinguish communicative problems in autism from those found in other clinical groups. This body of research has led to the consensus that children with autism are seriously limited in their communicative abilities [Lord and Paul, 1997; Tager-Flusberg, 1999] as evident in their restricted range of speech acts [e.g., Wetherby, 1986; Loveland et al., 1988] and impaired conversational and narrative skills [Loveland and Tunali, 1993; Tager-Flusberg, 1995; Tager-Flusberg and Sullivan, 1995]. Both theoretically and empirically these impairments have been directly related to theory of mind deficits. For example, Capps and colleagues [1998] found that among children with autism, the ability to respond in conversations with new relevant information was significantly correlated with performance on theory of mind tasks.

Conversational deficits in autism reflect fundamental problems in understanding that communication is about the expression and interpretation of intended rather than literal meaning [Happé, 1993]. Several studies have found that even older high-functioning people with autism have great difficulty interpreting videos of moving geometric forms, which are typically interpreted as social scripts, involving “human” characters with human attributes and motivations. Many of the adolescents with autism failed to view the visual stimuli within a social framework, and did not use mental state terms in their narrative descriptions. Baron-Cohen and colleagues have developed several new theory of mind related tasks, including the Eyes task, which tests a person’s ability to interpret mental states from the eye region of the face [Baron-Cohen et al., 1997], and a task that taps the ability to recognize faux pas in everyday social situations [Baron-Cohen et al., 1999]. The development of these tasks that are sensitive theory of mind problems in older individuals with autism will lead to clearer understanding of the range of deficits in social cognition among individuals with autism and how these deficits may link to their social difficulties in everyday life [Klin et al., 2000].
non-literal or figurative speech such as lies, sarcasm, or irony [e.g., Happé, 1993, 1994]. Pragmatic impairments in autism are found across different discourse contexts, such as personal narrative or story telling, and are closely related to theory of mind. What is striking about these impairments in communication is that they occur to some degree across the entire spectrum of autistic disorder. Across all ages, ability levels, and language levels, deficits are found in some or all of these aspects of pragmatics and communication. They are even considered to be one component of the broader autism phenotype, found among some proportion of first-degree relatives of individuals with autism [Landa et al., 1991, 1992].

In contrast to the universal nature of communicative deficits, language functioning in autism is much more variable. At one end, there are children whose vocabulary, grammatical knowledge, and articulation skills are well within the normal range of functioning, while at the other end a significant proportion of the population remains essentially non-verbal [Lord and Paul, 1997]. Less attention has been paid in recent years to these language deficits, though earlier studies suggested that children with autism might have greater difficulty with receptive language skills [Bartak et al., 1975].

One recent study investigated the profile of language abilities in a large group of children and adolescents with autism or Asperger syndrome [Jarrold et al., 1997]. Using a set of standardized tests, Jarrold and colleagues concluded that receptive abilities were not worse than expressive and, surprisingly, that there was no significant heterogeneity in the profile of language skills in autism. Following up on this study, Kjelgaard and Tager-Flusberg [2000] administered a battery of standardized language measures to a broader group of verbal children with autism, whose diagnoses were well documented. In contrast to the findings of Jarrold et al. [1997], Kjelgaard and Tager-Flusberg found significant heterogeneity in the language skills of the children with autism, although across all the children, articulation skills were spared. Different subgroups of children with autism were identified on the basis of their performance on the language measures. Some children had typical language skills (perhaps corresponding to the clinical impression of Asperger syndrome); for other children, language skills were significantly below age expectations. The profile of performance across the standardized measures for these language-impaired children was similar to the profile that defines the disorder of specific language impairment, including poorer performance on grammatical measures than on vocabulary tests and difficulty on a non-word repetition test [cf. Tager-Flusberg and Cooper, 1999]. Clearly more research is needed on these language deficits that are found in only some children with autism, especially given the significance of language as a key prognostic factor for this disorder [Ventner et al., 1992].

**Repetitive Behaviors and Interests**

Of the three primary diagnostic criteria for autism—social impairment, communication impairment and the presence of repetitive behaviors and interests—the social and communication criteria are closely related conceptually.

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(see earlier section on Social Cognition). The third criterion, however, is harder to relate to the first two [cf. Tager-Flusberg, 2001; Turner, 1997], and its various characteristics might not even be closely related to one another.

Several different types of behaviors are included in this criterion of repetitive behaviors and interests. First, there are the repetitive motor behaviors such as jumping up and down and flapping hands, that especially younger or less able children with autism display mainly when they are emotionally aroused. Second, there are repetitive activities that the children appear to find pleasurable, such as spinning car wheels or watching the same video repeatedly. Repetitive questions, verbal rituals, and complex motor sequences may also be an aspect of this kind of behavior, although these can be related more to anxiety than to pleasure. Children with autism may become distressed if interrupted and insist on finishing the sequence. It is for this reason that some children with autism meet DSM-IV criteria for obsessive-compulsive disorder, and it is this type of repetitive behavior that can be lessened by antidepressants [Lewis and Bodfish, 1998]. Third, there are children who have an intense interest in a particular topic such as heaters, train timetables, or dinosaurs. They may study the topic and become expert in it or simply want to see or be near an object of interest, depending on their overall ability.

In comparison to other characteristics of autism, little research has been done on this aspect of autistic behavior. To some extent this neglect may be because it is not viewed as a characteristic that is specific to children with autism; however, studies have demonstrated that repetitive behavior is significantly more common in autism than in comparison groups [Sztamari et al., 1989; Turner, 1997]. Recently Turner [1999] has argued that repetitive behavior in autism may be the direct reflection of impaired executive control. Turner’s studies on repetitive behavior found a significant correlation between parental reports of repetitive movements, activities, and circumscribed interests, with performance on tasks that tap perseveration, inhibitory control, and the ability to generate novel ideas [Turner, 1997]. More specifically, perseveration was most closely linked to repetitive movements, inhibitory control was related to generating novel ideas, while circumscribed interests was correlated with all the executive function tasks. Turner’s studies suggest that repetitive behavior can be explained as the result of a general disruption to executive processing systems that are used in generating and regulating novel and spontaneous behavior.

**GENETICS OF AUTISM**

Over the past few years considerable gains have been made in the search for genes that predispose to autism. It has been clear since the 1970s that autism is highly heritable, with heritability estimates over 90% [Santangelo and Folstein, 1999]. The recurrence risk for autism is around 6%-8%, compared with a population risk of 1/1,000 or less [Ritvo et al., 1989]. Combined data from three twin studies provide additional evidence. The concordance rate for autism among monozygotic twins is 65% while for dizygotic twins the concordance is 0% [Bailey et al., 1995].
This pattern of inheritance suggests oligogenic inheritance with epistasis. This means that there are probably a few (oligogenic), most likely 2–4, genes needed that interact with each other (epistasis) to cause the autism phenotype [Santangelo and Folstein, 1999]. Thus, in linkage studies, we would expect to find evidence for genes at more than one locus. To date, there is some evidence for three loci: chromosomes 7q, 13q, and 15q.

Currently a number of genetic studies are under way, using a variety of approaches. Several genetic linkage studies have now been published that have screened the entire genome, each including 60–100 families with affected sib pairs and their parents. Two of these studies have provided evidence for linkage to a region of chromosome 7q near the gene for cystic fibrosis [IMGSAC, 1998; CLSA, 1999]. These findings are of particular interest [cf. Ashley-Koch et al., 1999] because the linkage region overlaps with the region that has been identified in at least one study of specific language impairment [Fisher et al., 1998]. One study suggests a locus on chromosome 13q [CLSA, 1999], though this finding still awaits replication by other research teams. It has been known for a number of years that duplications of chromosome 15q 11-13 (the same region responsible for Prader–Willi and Angelman’s syndrome) are the most frequently reported chromosomal abnormality in autism [Baker et al., 1994]. One group has evidence for linkage in this region, and two others have reported positive results in association studies to markers in this region [Periccek–Vance et al., 1997]. Investigators are currently studying the DNA of autistic children who have chromosomal rearrangements with breakpoints in these regions, which are expected to offer further clues to the role of genes in this region in the etiology of autism.

Finally, on the basis of repeated observation of abnormal platelet serotonin in many children with autism, several investigators have been pursuing a candidate gene approach. Some evidence exists for an abnormality of the serotonin transporter gene, but this has been hard to pin down [Cook et al., 1998; Klauck et al., 1997]. Although research has yet to identify a specific gene associated with autism, considerable and rapid progress has been made in recent years. This is clearly one of the most promising areas of current research in the search for the biological causes of this disorder.

Family genetic studies of autism have also documented the presence of a range of conditions and characteristics in the non-autistic relatives of individuals with autism (see Piven [1999] for a recent review). The broader phenotype for autism includes documented history or presence of problems in all three domain that define autism: social, language and communication, and repetitive behaviors and interests [e.g., Bolton et al., 1994; Piven et al., 1997], but not for mental retardation, which is found in the majority of children with autism [Fombonne et al., 1997]. Parents of individuals with autism perform worse than controls on measures of executive function [e.g., Hughes et al., 1997], and subtle measures of theory of mind [Baron-Cohen and Hammer, 1997]. Studies also suggest that relatives of individuals with autism have elevated rates of psychiatric disorders, specifically major depression and anxiety disorders, that are independent of having a child with autism, and of other features of the broader autism phenotype [Bolton et al., 1998; Piven and Palmer, 1999].

These findings are particularly significant as they may be closely related to the social deficits that define the syndrome of autism.

These studies on the broader autism phenotype have important implications for our understanding of the biology of autism. The studies summarized here suggest that different genes, associated with independent features of the broader phenotype, contribute to the qualitatively different aspects of the symptoms of autism [Piven, 1999].

NEUROBIOLOGY OF AUTISM

Brain-imaging studies of autism have been carried out since 1980, first using X-ray computed tomography (CT), then more recently structural magnetic resonance imaging (MRI) and functional imaging using positron emission tomography (PET), functional MRI (fMRI), and other innovative technologies.

Structural Brain-Imaging Studies of Autism

Following Bauman and Kemper’s [1985] seminal neuropathological study on neuronal abnormalities in the Purkinje cells of the cerebellar hemispheres and limbic and paralimbic cortex, recent imaging studies focused on these regions of interest. To date, there have been more than 15 studies on the cerebellum in people with autism, with special focus on the cerebellar vermis, but the results have been quite inconsistent. Some studies report cerebellar hypoplasia [Courchesne et al., 1988], but these findings may be due to confounding effects of IQ or other variables [Levitt et al., 1999]. Filipek [1996] has criticized many of the earlier structural MRI studies of autism on methodological grounds. For example, these studies included individuals varying widely in age, sex, IQ, and language level who had not received rigorous diagnoses. Adequate control groups may not have been included, and the image quality and analyses were often quite limited.

Fewer studies have followed up on Bauman and Kemper’s [1985] interesting findings on cellular abnormalities in the areas of the limbic system, which found decreased neuronal size, increased neuronal packing density, and decreased complexity of dendritic arbors in hippocampus, amygdala, and other limbic structures, all suggesting developmental curtailment in the maturation of the neurons and neuropil. Aylward et al. [1999] recently conducted a well-designed study comparing the sizes of the amygdala and hippocampus in adolescent boys with autism who do not have mental retardation to those found in matched controls. The amygdala and hippocampal volumes were significantly smaller in the adolescents with autism, suggesting underdevelopment of the neural connections of limbic structures with other parts of the brain, particularly the cerebral cortex. These findings are particularly significant as they may be closely related to the social deficits that define the syndrome of autism.

A more consistent finding in the literature on autism is that the head size and brain size or volume are larger than expected in affected individuals [Piven et al., 1996; Lainhart et al., 1997; Deutsch et al., 1999]. Lainhart and colleagues [1997] suggest that this pattern of enlarged head size emerges after birth in early or middle childhood, though this finding awaits replication. Piven and colleagues [1996] found that the increase in cerebral volume in autism is attributable to posterior enlargement, but not increased frontal lobe size (see also Bailey et al., 1998). These findings on head and brain size in autism are extremely interesting as they may suggest further impor-
tient clues to the timing and nature of the neurodevelopmental abnormalities that underlie the clinical features of this disorder.

Finally, in a recent study Sears et al. [1999] conducted an MRI study focusing on the basal ganglia in a group of relatively high-functioning people with autism and a matched set of controls. The main findings were increased volume of the caudate nuclei in the participants with autism, which was proportional to the increased total brain volume and associated with compulsions and rituals, difficulties with change, and repetitive behaviors. The findings were replicated in a second study. The authors argue that the caudate could be part of an abnormal neural network that is involved in the repetitive behavior component of autistic disorder.

Functional Brain-Imaging Studies in Autism

Studies of functional brain activation in autism or Asperger syndrome are still in their infancy. Nevertheless, there have been a few exploratory studies, focusing particularly on regional activation patterns to socially relevant stimuli. Fletcher and colleagues [1995] conducted a PET study comparing activation patterns in healthy adults to stories requiring physical causal reasoning versus mental state reasoning. The mental state, or theory of mind, stories were associated with unique activation in regions of the left medial frontal cortex (Brodmann’s areas 8 and 9). In contrast, Happé and colleagues [1996], using the same paradigm with five adults with Asperger syndrome, found significantly less activation in this region for the mental state stories. Taken together, these studies of functional brain imaging provide an interesting and significant bridge between the studies of cognitive impairments in autism and the studies of brain pathology.

CONCLUSIONS

Research on autism has begun to clarify many aspects of this enigmatic and devastating neurodevelopmental disorder. Studies are being conducted at all levels of analysis, and we are beginning to see the interconnections between the underlying biological causes and the cognitive and behavioral manifestations of autistic disorder. The next decade will witness further developments, bringing us closer to a more comprehensive and integrated understanding of autism. Despite the exponential growth in basic studies on autism, there has been relatively little research on new treatments and interventions. It is hoped that our new knowledge about the core biological and cognitive deficits in autism will encourage more research on how to treat children and adults with autism, which is the ultimate goal of these endeavors.

REFERENCES


**CURRENT DIRECTIONS IN RESEARCH ON AUTISM**


