CHAPTER 8

Autism Spectrum Disorders

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Autism Spectrum Disorder is the term that is currently used to describe the broad range of pervasive developmental disorders. These disorders include Autistic Disorder, Asperger's Disorder (also referred to as Asperger's syndrome), Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS).

The Autism spectrum disorders involve impairments in reciprocal social interaction and communication and the presence of restricted, stereotyped, and repetitive interests and behaviors. Of these three symptom domains, impairments in social interaction are considered a primary feature of these disorders. These impairments include a lack of social and emotional reciprocity; atypical nonverbal behaviors such as atypical eye-to-eye gaze, facial expressions, body postures, and gestures to regulate social interaction;

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lack of interest and/or difficulty relating to others, particularly peers; and a failure to share enjoyment and interests with others. A great deal of heterogeneity exists among the Autism spectrum disorders in terms of the number and severity of symptoms across the three domains (social, communication, and stereotyped/restricted interests and behaviors) and in cognitive and adaptive functioning. Further, within each diagnostic category, impairments differ across individuals and, for any given individual, symptoms may change across the life span.

DIAGNOSIS, COURSE, AND PROGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (*DSM-IV;* American Psychiatric Association, 1994) and the *International Classification of Diseases,* 10th edition (*ICD-10;* World Health Organization, 1992) are two widely used systems for diagnosing Autism spectrum disorders. The specific criteria for each of the Autism spectrum disorders are described next.

Autistic Disorder

The diagnostic criteria for Autistic Disorder include at least six symptoms across three domains of functioning, with at least two symptoms in the area of social interaction, one in communication, and one in restricted interests and behaviors. Delays or abnormal functioning in at least one area—social interaction, language, symbolic or imaginative play—must be present before 3 years of age, and symptoms cannot be better accounted for by Rett's Disorder or Childhood Disintegrative Disorder (see following discussion). Individuals with Autism vary widely in symptom expression, cognitive level, and adaptive abilities. For a more detailed discussion, see the section on Symptom Presentation later in this chapter.

Asperger's Disorder

The characteristics that define Asperger's Disorder include intact formal language skills (e.g., vocabulary, grammar), with impairments in the social use of language and in nonverbal expression, social awkwardness, and idiosyncratic and consuming interests (Volkmar & Klin, 2001). Although motor clumsiness is not a defining feature of Asperger's Disorder, it is often observed (Volkmar & Klin, 2001). The *DSM-IV* diagnostic criteria for Asperger's Disorder include at least two symptoms in the domain of social interaction and one symptom in the domain of restricted interests and behaviors. Further, individuals with Asperger's Disorder do not demonstrate clinically significant delays in general cognitive ability, self-help skills, and adaptive development. Differentiating Asperger's Disorder and high-functioning Autism is often difficult to do clinically, and the empirical validity of such a distinction has not yet been unequivocally established (Ozonoff & Griffith, 2000; Volkmar & Klin, 2001).

Asperger's Disorder was included as a separate diagnostic category only in the more recent revisions of the *DSM-IV* and *ICD-10* classification systems, and epidemiologic data on this subtype of Autism Spectrum Disorder are scarce. The first systematic epidemiologic study of Asperger's Disorder was conducted in Sweden and yielded a prevalence rate of 28.5 per 10,000 (Ehlers & Gillberg, 1993). In a review of epidemiologic surveys, Fombonne and Tidmarsh (2003) concluded that the number of children with Autism was 5 times that of children with Asperger's Disorder, on average, suggesting that the prevalence of Asperger's is approximately 2 per 10,000. The authors note that future studies should focus on slightly older children (ages 8 to 12 years) as Asperger's Disorder is often diagnosed much later than Autism.

Rett's Disorder

Rett's Disorder occurs in 1 in 10,000 to 15,000 individuals, has been reported only in females, and involves a progressive deterioration of functioning between 6 and 18 months of age. Children with Rett's Disorder follow an apparently normal prenatal and perinatal period of development, with typical, early psychomotor development and normal head circumference at birth. This period of fairly typical development is followed by a gradual loss of speech and purposeful hand use and the development of microcephaly, seizures, autistic features, difficulties in coordinating gait or trunk movements, and stereotypic hand movements. Interest in social engagement diminishes in the first few years following onset, but may reemerge later. Individuals with Rett's Disorder have severe impairment in language development, severe psychomotor retardation, and severe to profound mental retardation. It was discovered that some cases of Rett's Disorder are caused by mutations in the gene (MECP2) encoding X-linked methyl-CpG-binding protein 2 (Amir et al., 1999).

Childhood Disintegrative Disorder

Childhood Disintegrative Disorder (CDD), also termed Heller's syndrome, is characterized by a marked regression in several areas of functioning following typical develop-

ment in the first 2 years of life. Regression can occur any time after the first 2 years and before age 10, but onset typically occurs before 4 years of age. This regression typically includes a loss of previously acquired skills in at least two of the following areas: expressive or receptive language, social abilities or adaptive behavior, bowel or bladder control, play, and motor skills. Individuals with this disorder also demonstrate impairments in two of the three domains that characterize Autism: social interaction, communication, and restricted, repetitive behavior.

Approximately 1 in 3 to 5 children with Autism are also reported to show a regression in language and social skills following a period of ostensibly typical development, but this regression generally occurs prior to 24 months of age. These children are classified as having Autism rather than Childhood Disintegrative Disorder. For a more detailed discussion of developmental course in Autism, see later discussion.

CDD is very rare and much less common than Autistic Disorder (*DSM-IV;* American Psychiatric Association, 1994).

Pervasive Developmental Disorder Not Otherwise Specified

A diagnosis of PDD-NOSis given when there exist clinically significant impairments in social interaction and/or communication, or restricted interests and behaviors are present, but criteria for a specific Autism Spectrum Disorder are not met. This usually occurs in cases where symptoms are present but are too few in number to meet criteria for a specific diagnosis. Similar to the other diagnostic categories, a diagnosis of PDD-NOS includes individuals of varying symptom severity, cognitive ability, and level of adaptive skills.

Differential Diagnosis and Comorbidity

Accurate diagnosis is critical for obtaining proper treatment and the best possible outcome. Therefore, it is important to understand how Autism spectrum disorders differ from other commonly diagnosed disorders of childhood and which conditions are comorbid with Autism.

Differentiating among the Autism Spectrum Disorders

Although the *DSM-IV* defines Autistic Disorder, Asperger's Disorder, and PDD-NOSpecified as separate disorders, children often receive different diagnoses within the Autism spectrum depending on the clinician and diagnostic instrument used to make the diagnosis. Although this can be confusing to parents and, in some cases, can impact a family's eligibility for federal- and state-mandated intervention services, treatment recommendations are essentially the same across the spectrum (see section on interventions later in this chapter).

Mental Retardation

Estimates of the percentage of individuals with Autism who also have mental retardation range from 75% to 89% (Filipek et al., 1999; Fombonne, 1999; Steffenburg & Gillberg, 1986) to 40% to 71% (Baird et al., 2000; Chakrabarti & Fombonne, 2001). More recent (lower) estimates may reflect an increase in diagnoses of higher-functioning individuals and/or effective early intervention.

Although approximately 75% of children with Autism also have mental retardation, the two disorders can be distinguished based on differences in a number of areas. Studies that have compared children with Autism to children with mental retardation of similar intellectual ability have shown that children with Autism often exhibit an uneven cognitive profile that is different from children with mental retardation. This pattern consists of higher scores on measures of visual-spatial skills and auditory rote memory and lower scores on verbal comprehension (Happe, 1994; Lockyer & Rutter, 1970). In addition, a number of studies have identified differences between children with Autism and children with mental retardation in nonverbal communication skills, motor imitation, social cognition, play, and emotion recognition and expression (see Symptom Presentation section later in this chapter). Similarities include simple motor stereotypes, including self-injurious behaviors, which appear to be a function of mental age rather than diagnosis (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Wing, 1978).

Due to the high comorbidity of Autism and mental retardation, the individual's developmental level and a thorough knowledge of typical developmental milestones is critical to making an accurate diagnosis.

Specific Language Impairment

All children with Autism have deficits in the communicative use of language (Lord & Paul, 1997; Tager-Flusberg, 1999; Wilkinson, 1998), and most have impairments as well in the formal aspects of language, such as vocabulary, complex syntax, and morphology, similar to those shown by children with specific language impairment (SLI)[1] (Bartak, Rutter, & Cox, 1975; Bishop, North, & Donlan, 1996;

[1] SLI is a developmental language disorder that refers to below-average performance on standardized language tests in the absence of other disorders, such as mental retardation or hearing loss.

Dollaghan & Campbell, 1998; Gathercole & Baddeley, 1990; Tager-Flusberg & Cooper, 1999). Thus, Autism and SLI appear to be distinct disorders but highly comorbid. Research has compared the language profiles of children with Autism to those of children with SLI and found striking similarities. Children with Autism (ages 4 to 14 years) were given a language battery to assess phonological, lexical, and higher-order semantic and grammatical language skills (Kjelgaard & Tager-Flusberg, 2001). The sample was then divided into three groups based on their overall scores on the battery: normal, borderline, and impaired language. Children with impaired language demonstrated language profiles that were very similar to those previously observed in children with SLI, including better vocabulary relative to higher-order language abilities, poor performance on phonological processing (nonword repetition test), and difficulties in marking tense. This same group of researchers then examined the brain structure of children with Autism using magnetic resonance imaging (MRI), focusing specifically on the language regions of the cortex. Similar to children with SLI, the children with Autism showed larger right cortical regions relative to left regions, unlike controls, who showed larger left regions. These authors conclude that there is a subtype of children with Autism with the same neurocognitive phenotype as children with SLI. Genetic studies provide further clues to a shared genetic basis of these two disorders (see section on Etiology).

Nonverbal Learning Disability

Nonverbal learning disability (NLD) is characterized by lower nonverbal skills (i.e., visual-spatial, mathematics, handwriting) relative to verbal skills. Children with NLD also tend to be clumsy and exhibit social difficulties. Many children with Asperger's Disorder and some children with high-functioning Autism also meet criteria for NLD and may benefit from special educational services aimed at improving math and motor skills (Ozonoff, Dawson, & McPartland, 2002).

Tic Disorders

Many individuals with Autism exhibit stereotypic movements or vocalizations that are considered to be volitional and do not cause distress to the individual. Tics, however, refer to sudden, rapid, recurrent, stereotypical movements or vocalizations that cause marked distress to the individual and are generally believed to be involuntary. A study of 447 individuals with Autism spectrum disorders reported the presence of tics in more than 30% of the sample, with 4.3% meeting criteria for a specific tic disorder, Tourette's syndrome (Baron-Cohen, Scahill, Izaguirre, Hornsey, & Robertson, 1999). An additional 2.2% were diagnosed with probable Tourette's syndrome, yielding a combined rate of 6.5%, which is greater than the general population risk. These results suggest an increased risk for tic disorders in individuals with Autism, although larger-scale epidemiological studies are needed.

Attention-Deficit/Hyperactivity Disorder

One of the most common initial misdiagnoses, particularly for children with high-functioning Autism and Asperger's Disorder, is Attention-Deficit/Hyperactivity Disorder (ADHD; Ozonoff et al., 2002). Children with ADHD show difficulties sustaining attention and organizing tasks, are easily distracted, often do not seem to listen when spoken to, exhibit an excessive activity level, interrupt others, and talk excessively. Many children with Autism and Asperger's Disorder exhibit these same symptoms, but for very different reasons. For instance, due to the significant social and executive function deficits in Autism, these children may not seem to be listening when spoken to and may interrupt others, talk excessively, and show difficulty in organizing tasks and following through on assignments. Key distinguishing features of Asperger's Disorder are profound difficulties in social interaction and the presence of preoccupations and restricted range of interests.

Obsessive-Compulsive Disorder

Children with Autism often exhibit an insistence on routines and rituals and a high need for order, which may be confused with Obsessive-Compulsive Disorder (OCD; Ozonoff et al., 2002). Most children with OCD experience their behavior as intrusive and odd and wish that they could stop performing the behaviors. They also experience anxiety that is alleviated by engaging in the behaviors. In contrast, children with Autism have little insight into the nature of their repetitive and ritualistic behaviors, do not realize that the behaviors may be considered odd, and do not try to stop engaging in them. In addition, the need for routine and order in Autism is only one in a constellation of symptoms that characterize the disorder. In some cases, an individual may suffer from both Autism and OCD. Comorbid diagnosis of Autism Spectrum Disorder and OCD ranges from 1.5% to 29% (Lainhart, 1999). In such cases, treatment should address both disorders.

Other Anxiety Disorders

Symptoms of anxiety are frequently observed in children across the Autism spectrum, making it difficult to determine whether these symptoms represent a truly separate disorder. Nevertheless, Lainhart (1999) estimated a 7% to

84% comorbid rate of anxiety disorders in individuals with Autism, with Generalized Anxiety Disorder, agoraphobia, separation anxiety, and simple phobia being the most common. Symptoms of anxiety can often be ameliorated by medication and/or appropriate behavioral interventions (see section on interventions later in this chapter).

Depression

Depression is commonly comorbid with Autism, occurring at rates ranging from 4% to 58% (Lainhart, 1999). Although symptoms of depression occur most frequently in adolescents and adults with Asperger's Disorder or PDD-NOS, they can occur in children (Ghaziuddin & Greden, 1998; Wozniak et al., 1997). Primary symptoms are not always related to mood and may include increased agitation, aggression, self-injurious behavior, increased engagement in compulsive and repetitive behaviors, social withdrawal, changes in sleep and appetite, and general deterioration in functioning (Howlin, 1997; Lainhart & Folstein, 1994). Major Depression in individuals with Autism is often ameliorated by antidepressant therapy (Lainhart & Folstein, 1994).

Seizure Disorders

Individuals with Autism are at increased risk for developing seizure disorders, with prevalence rates ranging from 5% to 39% (Ballaban-Gil & Tuchman, 2000; Tidmarsh & Volkmar, 2003) and age of onset either before 3 years of age or, more frequently, during puberty (11 to 14 years; Gillberg & Steffenburg, 1987; Goode, Rutter, & Howlin, 1994; Rutter, 1970; Volkmar & Nelson, 1990). Seizure disorders are more common in very low-functioning individuals (i.e., IQ of less than 50) and in females (Rutter, 1984; Volkmar & Nelson, 1990). In addition, epileptiform abnormalities without evidence of clinical seizures are also common (one study reported 21% of 392 children) in Autism (Tuchman & Rapin, 1997).

Early Identification

Some parents of children with Autism report being concerned about their child's development since birth, and, by 18 months, most parents raise concerns with their primary health care provider (Howlin & Asgharian, 1999; Rogers, 2001; Siegel, Pilner, Eschler, & Elliot, 1988). However, the age at which a diagnosis is confirmed tends to be much older. In a survey of 770 parents of children with Autism and Asperger's Disorder, the *average* age at which a formal diagnosis was confirmed was 5.5 years for Autism and 11 years for Asperger's Disorder (Howlin & Asgharian, 1999). Refining methods of early identification and diagnosis allows for early intervention and better outcomes for young children with these disorders.

Reliability and Stability of Early Diagnosis

Research indicates that symptoms of Autism are often present during infancy and that Autism spectrum disorders can be detected as early as 18 months of age and reliably diagnosed by 20 to 24 months (Baron-Cohen et al., 1996; Rogers, 2001). Further, there is now evidence that a diagnosis of Autism at age 2 remains stable over time. For instance, Lord (1995) found that 14 of 16 children receiving a clinical diagnosis of Autism at age 2 received an independent clinical diagnosis of Autism at age 3. Baron-Cohen et al. reported that 10 out of 10 children diagnosed with Autism at 18 to 20 months retained the diagnosis at 3.5 years. W. L. Stone et al. (1999) showed that 96% of the children in their study retained a diagnosis of Autism or PDD-NOS from age 2 to 3. Others have shown that diagnosis of Autism spectrum disorders in children under 3 years of age is reliable across clinicians, although less so when distinguishing Autism from PDD-NOS (W. L. Stone et al., 1999; Volkmar, Szatmari, & Sparrow, 1993).

Early Symptoms

Previous studies have identified a number of characteristics that distinguish preschool and early elementary school-age children with Autism from those with developmental delay. These include impairments in joint attention, imitation, symbolic play, and responses to emotion (e.g., Charman & Baron-Cohen, 1997; Charman et al., 1998; G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; G. Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Mundy, Sigman, Ungerer, & Sherman, 1986; W. L. Stone, Ousley, & Littleford, 1997; W. L. Stone et al., 1999). Relatively few controlled studies, however, have examined how children with Autism below age 3 differ from children with related disabilities, such as developmental delays, and most of these have relied on observations made from home videotapes (e.g., Baranek, 1999; Osterling, Dawson, & Munson, 2002). Charman et al. (1998) found that 20-month-olds with Autism were more impaired in joint attention, responses to another's distress, pretend play, and imitation, compared to those with language delay. Other studies found that 24-month-olds with Autism performed fewer joint attention gestures, including pointing and showing, and had more impaired language and imitation skills than typically developing and language impaired children (Lord & Paul, 1997; W. L. Stone et al., 1997).

Retrospective studies of home videotapes have been an especially fruitful area of research. Using this method, investigators have been able to observe the early social, language, motor, and play behaviors of infants who later receive a diagnosis on the Autism spectrum and to examine developmental differences between infants with Autism and typically developing infants (Mars, Mauk, & Dowrick, 1998; Osterling & Dawson, 1994) and infants with mental retardation (Baranek, 1999; Osterling & Dawson, 1999). In one such study, Osterling and Dawson (1994) examined videotapes of 1st birthday parties and demonstrated that 1-year-olds later diagnosed with Autism could be distinguished from 1-year-old typically developing infants. How often a child looked at the face of another person (gaze) correctly classified the greatest number of children (77%). When gaze was combined with the behaviors of showing, pointing, and orienting to name (i.e., social orienting), 91% of the infants with typical development and with Autism were correctly classified. These results were replicated by Mars et al., who used blind scoring to evaluate home videotapes of 1st birthday parties of 25 infants later diagnosed with Autism and 25 typically developing infants. Again, the variable "looks at faces" was found to be a powerful discriminator between the two groups, as well as joint attention (e.g., pointing) behaviors.

A subsequent home videotape study compared 1-year-olds later diagnosed with an Autism Spectrum Disorder (ASD) with 1-year-olds later diagnosed with mental retardation and 1-year-olds with typical development. This study showed that 1-year-olds with ASD could be distinguished not only from typical 1-year-olds, but also from 1-year-olds with mental retardation (Osterling et al., 2002). This is important due to the high comorbidity of Autism and mental retardation. In this study, the infants with ASD were less likely to look at others and to orient to their name than were infants with mental retardation. Joint attention behaviors, however, did not distinguish between ASD and developmental delay at 1 year of age, suggesting that other behaviors related to attending to people and other's speech might be important in distinguishing ASD from developmental delay at very young ages. In yet another home videotape study, a failure to orient to name was the best discriminator between 8- to 10-month-olds with ASD versus typical development (Werner, Dawson, Osterling, & Dinno, 2000). Again, joint attention did not distinguish the two groups at this young age.

Screening Instruments

A number of promising early screening methods have been developed to detect symptoms of Autism in infants and toddlers, including the Checklist for Autism in Toddlers (CHAT; Baron-Cohen, Allen, & Gillberg, 1992), the Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001), the Pervasive Developmental Disorders Screening Tests (PDDST; Siegel & Hayer, 1999), and the Screening Tool for Autism in Two Year Olds (STAT; W. L. Stone, Coonrod, & Ousley, 2000). However, none of these instruments are currently in widespread use. The CHAT, a parent report and behavioral observation measure, has been shown to have high specificity (98%) but low sensitivity (38%), suggesting that it is not adequate for screening in public health settings (Baird et al., 2000). More promising results have been shown for the M-CHAT, a parent report measure, with a specificity of 95% and a sensitivity of 97% (Robins et al., 2001). The PDDST differs from the CHAT and the M-CHAT in that it offers different versions for primary care clinics, developmental clinics, and Autism specialty clinics. The primary care version yielded a sensitivity of 85% and specificity of 71% (Siegel & Hayer, 1999). The STAT is still under development but has been shown to discriminate well between children with Autism and other developmental disorders in a small sample of 2-year-olds (W. L. Stone et al., 2000).

It is likely that screening methods currently under development will continue to need refinement. This refinement will depend on research aimed at identifying early emerging behaviors that can distinguish very young children with Autism from those with related disabilities, such as developmental delay. Behaviors such as joint attention, gestures, verbal language, and pretend play may have limited utility in distinguishing infants and toddlers with Autism from those with developmental delay as these behaviors are not normally present until 1 to 2 years of age; 18- to 24-month-old toddlers with significant developmental delay would not be expected to show these behaviors.

Developmental Course

There are generally two patterns of symptom development in Autism. The most common course involves the emergence of symptoms in the 1st year of life. In roughly a third of cases, however, there is a regression in skills following a period of fairly typical development.

Early Onset

Symptoms of Autism typically emerge early, within the first 12 months of life. This pattern of symptom development is referred to as early-onset Autism. Both parent report (Lord, 1995) and home videotape studies (Baranek, 1999; Osterling & Dawson, 1994; Werner et al., 2000;

Werner, Dawson, & Munson, 2001) have confirmed that for many children with Autism, symptoms may emerge as early as 8 months of age.

Regression

Symptoms of Autism may also appear after a period of fairly typical development, with a regression or loss of previously acquired skills generally occurring prior to 24 months of age. This pattern of symptom emergence in Autism has been estimated to occur in 20% to 47% of cases (e.g., Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Kurita, 1985; Lord, 1995; B. A. Taylor et al., 2002), with typical age of onset ranging from 16 months (B. J. Williams & Ozonoff, 2001) to 24 months (Davidovitch et al., 2000). Primarily, there is a loss of language skills, although losses can occur in social interest and responsiveness, nonverbal communication, cognitive ability, and self-help/adaptive behavior. Osterling and Dawson (1999) examined home videotapes of children with reported regression and found that, indeed, these children displayed typical social and communication behaviors at 1 year of age. However, using retrospective parent report, two other studies have shown that approximately 50% of the children who were reported to have lost skills after 1 year of age actually showed a delay in skills prior to the reported regression (Werner et al., 2001; B. J. Williams & Ozonoff, 2001). Werner and colleagues found that children with versus without a history of early regression did not differ in language, cognitive, or symptom outcome at age 3 to 4 years (Werner, Dawson, Munson, & Osterling, in press).

Autism across the Life Span

Although Autism is considered to be a lifelong disorder, the specific constellation of symptoms and the severity of those symptoms tend to fluctuate across development (Lord, 1997). One study reported improvements from age 5 in social and communication skills and in repetitive behaviors in a sample of 38 adolescents and young adults, with 13% of the sample no longer meeting criteria for Autism (Piven, Harper, Palmer, & Arndt, 1996).

With such changing patterns and severity of symptoms, both current and historical reports of symptoms are often required to make an accurate diagnosis and for inclusion in genetic studies of Autism. The Autism Diagnostic Interview-Revised (Le Couteur, Lord, & Rutter, 2003; Lord, Rutter, & Le Couteur, 1994) is a standardized, semistructured parent interview that provides both a current and a lifetime diagnosis for individuals with a mental age of 18 months or greater. However, it relies on retrospective parent report and should therefore be combined with other sources of information, such as behavioral observation, in making a diagnosis. One such behavioral measure that is widely used is the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000; Lord, Rutter, DiLavore, & Risi, 1999; Lord, Rutter, Goode, & Heemsbergen, 1989), designed to assess individuals at varying stages of development and language level, from nonverbal children to high-functioning adults (there are four modules in all). The ADOS is a standardized, semistructured play interaction that provides opportunities for reciprocal social interaction, communication, and imaginative play and can be used across a wide range of chronological and mental ages (normative data exist for ages ranging from 15 months to 40 years).

Prognosis

Although the diagnosis of Autism tends to be quite stable into adolescence and adulthood, outcome is more varied. For as many as 75% of individuals with Autism, outcome tends to be poor. However, fair to good outcomes (i.e., adequate functioning in social, work, and school domains) are observed in at least 25% of individuals (Gillberg & Steffenburg, 1987; Nordin & Gillberg, 1998; Sigman & Norman, 1999). A more recent study that followed children with Autism from age 2 to age 9 found that as many as 40% obtained good outcomes based on language and cognitive scores (W. L. Stone, Turner, Pozdol, & Smoski, 2003). Although outcome is typically best for individuals with normal to near-normal intelligence, it is still lower than expected based on general intellectual ability. For instance, many individuals with Autism who have normal intelligence nevertheless require supervised living arrangements, are employed in low-level jobs, and do not develop friendships or marry (Tsatsanis, 2003). Compared to earlier studies (i.e., prior to 1980), however, there is evidence of better outcome in Autism in more recent years (Howlin & Goode, 1998). Improved outcome is likely related to availability of early and appropriate interventions.

Predictors of Outcome

Identifying specific factors that predict outcome in Autism is of critical importance for both researchers and clinicians and can lead to improved, targeted early interventions. IQ above 50 and language (specifically, meaningful speech by 5 to 6 years of age) remain the strongest predictors of positive outcomes for these children (Bartak & Rutter, 1976; Gillberg, 1991; Gillberg & Steffenburg, 1987; Lincoln, Courchesne, Kilman, Elmasian, & Allen,

1988; Lockyer & Rutter, 1970). Early language ability has been shown to predict both academic achievement and social competence (Howlin, Mawhood, & Rutter, 2000; Venter, Lord, & Schopler, 1992). In addition, a number of studies have indicated that early, intensive behavioral intervention is associated with higher IQ scores, a greater likelihood of developing language, and an increased chance of being placed in a regular education classroom (G. Dawson & Osterling, 1997; Lord & Schopler, 1989; Lovaas, 1987; McEachin, Smith, & Lovaas, 1993; Sigman & Ruskin, 1999).

Other predictors of language and social outcome include total speech and language therapy received, early expressive language ability, imitation and joint attention abilities, social interaction and shared affect, toy play, and age of diagnosis, with earlier diagnoses relating to poorer outcomes (Rogers & Hepburn, 2003; W. L. Stone et al., 2003; Toth, Dawson, Munson, Estes, & Abbott, 2003). Of particular importance, gains in verbal IQ have been observed in children with Autism beyond the preschool years (Lord, DiLavore, Shulman, Risi, & Pickles, 2003; Nordin & Gillberg, 1998; W. L. Stone et al., 2003).

EPIDEMIOLOGY

Autism was once believed to be a rare disorder, occurring at a rate of 4 to 5 in 10,000. In recent years, however, reported cases of Autism have increased significantly, leading to both public and scientific debate as to whether these estimates reflect a true increase in the number of children with this disorder, or increased awareness and detection along with a broadening definition of Autism.

Prevalence

The prevalence of Autism spectrum disorders has increased significantly in the past few decades. A large epidemiological study conducted by the Centers for Disease Control (CDC) found a prevalence rate of 34 per 10,000 among 3- to 10-year-old children in metropolitan Atlanta (Yeargin-Allsopp et al., 2003). One of the strengths of this study was sample size: 987 confirmed cases, compared to many previous studies with a median sample size of 50 (Fombonne, 2003). However, this rate of 34 per 10,000 is likely to be an underestimate. Higher-functioning individuals may have been missed, and younger children may not have been identified. Fombonne suggests that the rate reported for 5- to 8-year-olds in the CDC study—of 41 to 45 in 10,000—may be more accurate and is similar to other surveys that report a prevalence rate of 60 per 10,000 (Baird et al., 2000; Bertrand et al., 2001; Chakrabarti & Fombonne, 2001; Fombonne, 2003). There has been public debate about a possible epidemic of Autism as rates are 3 to 4 times higher than in the 1970s. However, this apparent rise in rates may be, in part, the result of a broadening definition of Autism, particularly at the less severe end of the spectrum; methodological differences in surveys of prevalence, particularly in methods for case finding (e.g., relying on single versus multiple sources for case identification); and an increasing use of the diagnosis of Autism so that families can take advantage of federally mandated early intervention programs (Fombonne, 2003).

Gender

Autism affects males at rates 3 to 4 times higher than females (Fombonne, 1999; Volkmar et al., 1993; Yeargin-Allsopp et al., 2003). However, when females are affected, they more often fall in the severe mental retardation range (IQ < 35) and exhibit more severe symptomatology than males with the disorder (Volkmar et al., 1993). Further, the recurrence risk rate for siblings of females with Autism is twice that of siblings of males with Autism (Jorde et al., 1990).

Socioeconomic Status and Culture

Autism affects individuals at all socioeconomic levels (Fombonne, 1999, 2003; Steffenburg & Gillberg, 1986; Wing & Gould, 1979) and in all parts of the world, including Canada (Bryson, Clark, & Smith, 1988), England (Chakrabarti & Fombonne, 2001; Wing & Gould, 1979), France (Cialdella & Mamelle, 1989; Fombonne, Bolton, Prior, Jordan, & Rutter, 1997), Sweden (Steffenburg & Gillberg, 1986), Norway (Sponheim & Skjeldal, 1998), Iceland (Magnusson & Saemundsen, 2001), Japan (Honda, Shimizu, Misumi, Nimi, & Ohashi, 1996; Sugiyama & Abe, 1989), Hong Kong (Chung, Luk, & Lee, 1990), Russia (Lebedinskaya & Nikolskaya, 1993), and Croatia (Bujas-Petkovic, 1993).

SYMPTOM PRESENTATION

Symptoms of Autism include impairments in the broad domains of social interaction, play, language and communication, and a restrictive range of interests and activities.

Specific symptoms in each of these broader domains are described next.

Impairments in Social Interaction

Although symptom presentation varies widely across individuals and across the life span, impairments in social attention are a primary early feature of the disorder. It has been hypothesized that a lack of normal attention to social stimuli, such as faces, voices, and emotional expressions, deprives the child with Autism of social information input during the 1st years of life, disrupting normal brain and behavioral development as well as subsequent social development (Mundy & Neal, 2001). Such impairments in social attention, particularly joint attention skills, are believed to also impede the development of language (Bono, Daley, & Sigman, 2003; Carpenter, Nagell, & Tomasello, 1998; G. Dawson, Toth, et al., 2004; Mundy, Sigman, & Kasari, 1990; Rogers & Hepburn, 2003; Sigman & Ruskin, 1999; Tomasello & Farrar, 1986).

One theory that has been proposed to explain the social attention impairments in Autism is that these impairments are the result of an underlying impairment in social motivation, or a failure to find social stimuli inherently rewarding (G. Dawson, Toth, et al., 2004; G. Dawson, Webb, et al., 2002; Mundy & Neal, 2001). According to this view, the preferential attention to social stimuli (faces, emotional expressions, voices) that is typically present very early in life is most often accompanied by affective sharing between infant and caregiver. This mutual exchange of positive affect during episodes involving eye contact is inherently rewarding to the typically developing toddler and serves to motivate the child to notice and attend to social and affective cues. It is hypothesized that the child with Autism fails to find eye-to-eye gaze inherently rewarding and is therefore less motivated and less likely to attend to social stimuli, make meaning out of others' emotional expressions, and participate in early social exchanges. As a result, the child with Autism has fewer opportunities to engage in acts that allow for the acquisition and development of social communication and language skills.

Social Orienting Impairments

Perhaps the first social attention impairment in Autism is a lack of normal "social orienting," namely, the tendency to spontaneously orient to naturally occurring social stimuli in one's environment (G. Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). In typical development, infants devote particular attention to social stimuli, including faces, voices, and other aspects of human beings (Rochat & Striano, 1999). Indeed, by 6 months of age, typically developing infants will actively orient (i.e., turn head and/or eyes) to novel stimuli, particularly social stimuli (e.g., being called by name; Trevarthen, 1979). Children with Autism, however, exhibit early impairments in social orienting. Home videotape studies of infants later diagnosed with Autism (Osterling & Dawson, 1994; Osterling et al., 2002; Werner et al., 2000) revealed social attention impairments, including a failure to look at others and orient to their name in 12-month-olds, and a failure to orient to name in 8- to 10-month-old infants. In two experimental studies of preschool children with Autism and mental age-matched children with developmental delay, children with Autism more frequently failed to orient to both social and nonsocial stimuli, but the impairment was more severe for social stimuli (G. Dawson, Meltzoff, & Osterling, 1995; G. Dawson, Toth, et al., 2004).

Joint Attention

Joint attention behaviors include sharing attention to an object or event (e.g., through the use of alternating eye gaze), following the attention of another (e.g., following a gaze or point), and directing attention (e.g., showing and pointing to objects/events). Some infants display some aspects of joint attention (e.g., matching direction of mother's gaze to a visible target) as early as 6 months of age (Morales, Mundy, & Rojas, 1998), and most infants display all of these skills by 12 months of age (Carpenter et al., 1998; Leekam & Moore, 2001). Research has established joint attention ability as a core social-communication impairment in children with Autism, present by 1 year of age and incorporated into the diagnostic criteria for the disorder (Mundy et al., 1986; *DSM-IV,* American Psychiatric Association, 1994). Impairments in joint attention skills have been found to distinguish preschool-age children with Autism from those with typical and delayed development (Bacon, Fein, Morris, Waterhouse, & Allen, 1998; Charman et al., 1998; G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; G. Dawson, Munson, et al., 2002; Mundy et al., 1986). Additionally, impairments in protodeclarative joint attention behaviors (e.g., pointing to show, sharing) seem to be more severe than impairments in protoimperative joint attention behaviors (e.g., pointing to make a request) in children with Autism (Mundy et al., 1986, 1990; Sigman, Mundy, Sherman, & Ungerer, 1986). Joint attention ability is predictive of both concurrent language ability and future gains in expressive language skills for children with Autism (Mundy et al., 1990; Mundy, Sigman, Ungerer, & Sherman,

1987; Sigman & Ruskin, 1999; Toth et al., 2003). Taken together, these findings suggest that joint attention ability is a pivotal skill in Autism as it appears to lay a foundation for the development of more complex abilities, such as pretend play, language, and theory of mind (Charman, 1997, 2003; Mundy & Crowson, 1997; Sigman, 1997).

Face Recognition

At birth, typically developing infants display a visual preference for the sounds, movements, and features of the human face (Goren, Sarty, & Wu, 1975; Maurer & Salapatek, 1976; Morton & Johnson, 1991). Very early in life, infants are not only able to recognize their mother's face (Bushnell, Sai, & Mullin, 1989), but they can also discriminate some facial expressions (Nelson, 1993). Children with Autism, however, do not show this same preference for and fascination with faces. Osterling and Dawson (1994) found in a study of home videotapes that a failure to look at others' faces best discriminated 12-month-olds with Autism from 12-month-old typically developing infants.

Face matching and face recognition impairments have been found across a number of studies in both children and adults with Autism (Boucher & Lewis, 1992; Boucher, Lewis, & Collis, 1998; Cipolotti, Robinson, Blair, & Frith, 1999; Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998; Jambaque, Mottron, Ponsot, & Chiron, 1998; Klin et al., 1999; Ozonoff, Pennington, & Rogers, 1990; Tantam, Monaghan, Nicholson, & Stirling, 1989; Teunisse & DeGelder, 1994). Using electrophysiological measures, G. Dawson and colleagues (G. Dawson, Carver, et al., 2002; McPartland, Dawson, Carver, & Panagiotides, 2001a, 2001b) showed that 3- to 4-year-old children with Autism failed to show a differential brain electrical response to mother's versus stranger's face, as did children with delayed and typical development. Interestingly, however, the children with Autism did show greater event-related potential (ERP) responses to the familiar versus unfamiliar object, similar to the pattern of responses shown by chronological age-matched typical children. This finding suggests that, in children with Autism, the recognition memory impairment is specific to faces and that this impairment is present by at least 3 years of age.

Other studies have shown that individuals with Autism process faces differently from controls (Celani, Battacchi, & Arcidiacono, 1999; Davies, Bishop, Manstead, & Tantam, 1994). For example, whereas typically developing individuals tend to focus on the eyes when processing faces, individuals with Autism often focus on the mouth (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Klin et al., 1999; Langdell, 1978). Additionally, individuals with Autism do not show the typical difficulty in processing inverted as opposed to upright faces (Hobson, Ouston, & Lee, 1988; Langdell, 1978; McPartland et al., 2001a, 2001b). In a recent ERP study, high-functioning adolescents and adults with Autism were shown to exhibit longer latencies of the N170 (face-specific) ERP component as compared to IQ-matched adolescents and adults. In addition to overall slower processing of face stimuli, the individuals with Autism showed similar ERP patterns in response to upright versus inverted faces and did not show the right-lateralized ERP that is found in typical individuals (McPartland et al., 2001a, 2001b).

Functional magnetic resonance imaging (fMRI) techniques have also been used to study face processing in Autism. Schultz et al. (2000) found that when individuals with Autism were shown pictures of faces, they showed less activation in the fusiform gyrus, a specialized region of the brain devoted to face processing, than in the inferior temporal gyri, a region of the brain that is typically used to process objects. Future research is needed to explore the connection between abnormalities in face processing and other social attention impairments in Autism.

Emotion Recognition and Expression

In typical development, infants are able to recognize and express emotions at a very young age. At 6 months of age, infants respond differentially to happy versus sad expressions (Cohn, Campbell, Matias, & Hopkins, 1990; Termine & Izard, 1988). At 12 months, infants are able to modulate their own behavior in response to the emotions expressed by their mother, approaching an object when mother displays a joyful expression but not when she displays a fearful expression (Klinnert, Campos, Sorce, Emde, & Svejda, 1983). By the end of the 2nd year of life, children are beginning to talk about emotions and can label simple emotions, such as happy, mad, and sad (Bretherton & Beeghly, 1982; Smiley & Huttenlocher, 1989). Children with Autism, however, generally do not exhibit this typical pattern of emotional development. A number of studies have shown that children with Autism are impaired on tasks requiring recognition and matching of emotional faces and responding to the emotional displays of others (Bormann-Kischkel, Vilsmeier, & Baude, 1995; Celani et al., 1999; G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; G. Dawson, Toth, et al., 2004; Hobson, Ouston, & Lee, 1989; Loveland et al., 1997; Sigman, Kasari, Kwon, & Yirmiya, 1992; Sigman, Ungerer, Mundy, & Sherman, 1987). Baron-Cohen, Spitz, and Cross (1993) reported that children with Autism are able to recognize simple emotions, such as happy and sad, which are typically caused by situations, but show

greater difficulty than controls in recognizing surprise, which is typically caused by beliefs. Others, however, have shown that emotion recognition impairments may not be specific to Autism, but related rather to verbal memory and performance IQ (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999). In a study of children and adolescents ages 8 to 18, no differences were found between children with Autism and age- and verbal IQ-matched ADHD controls on emotion matching and emotion recognition tasks (Buitelaar et al., 1999).

In one of the earliest studies of emotional expression in Autism, children with Autism were found to exhibit significantly more negative emotions as well as incongruous blends of emotion as compared to typical controls (Yirmiya, Kasari, Sigman, & Mundy, 1989). Further, children with Autism failed to show positive affect even in situations where positive affect is typically displayed, such as in joint attention interactions (Kasari, Sigman, Mundy, & Yirmiya, 1990). Dawson, Hill, Spencer, Galpert, and Watson (1990) examined mother-child interactions and found that children with Autism smiled as frequently as receptive language age-matched typically developing children, but were less likely to combine smiles with eye contact or to smile reciprocally. These authors proposed that children with Autism may have a specific impairment in their ability to engage in affective sharing experiences. When talking about emotion, children with Autism required more time and more prompts, and their responses were more scripted, as compared to age-matched typically developing controls (Capps, Yirmiya, & Sigman, 1992). Finally, although individuals with Autism are able to spontaneously display facial expressions, Loveland et al. (1994) reported that they showed a particular difficulty producing affective expressions upon request without a model.

Many studies that have assessed emotion perception in children with Autism have required language, making results difficult to interpret. G. Dawson and colleagues (G. Dawson, Webb, Carver, Panagiotides, & McPartland, 2004) used ERPs to determine whether 3- to 4-year-old children with Autism Spectrum Disorder exhibited differential brain responses to a fear versus a neutral facial expression, present in typical development by 7 months of age. It was found that children with ASD did not show the typical difference in amplitude of an early ERP component to the fear versus neutral face, indicating early differences in neural processing of emotion in Autism.

Imitation

Meltzoff and Moore (1977) demonstrated that newborns are able to imitate facial expressions, which suggests that this is an innate ability. Children with Autism, however, show impairments in both immediate and deferred motor imitation (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Sigman & Ungerer, 1984; W. L. Stone et al., 1997). Of particular importance, imitation skills in children with Autism have been shown to predict later social and language learning (Charman et al., 2000, 2003; W. L. Stone et al., 1997; W. L. Stone & Yoder, 2001). In one study, body imitation was found to predict expressive language ability, whereas object imitation predicted play skills (W. L. Stone et al., 1997). Additionally, it has been theorized that a failure to engage in social imitative play may interfere with the development of joint attention, social reciprocity, and later theory of mind abilities (G. Dawson, 1991; Meltzoff & Gopnick, 1993; Rogers & Pennington, 1991).

Theory of Mind

The ability to infer mental states, including intentions, memories, and beliefs, and to then use this information to understand and predict the behavior of others is "one of the quintessential abilities that makes us human" (Baron-Cohen, 2000, p. 3; see also Whiten, 1993). This ability is referred to as "theory of mind" and typically develops between 3 and 5 years of age (Flavell, 1999; Wellman, 1993; Wellman, Cross, & Watson, 2001). Children with Autism, however, show impairments on standard theory of mind tasks, such as false-belief tasks that require the child to infer what another person will think or do (Baron-Cohen, 2000; Baron-Cohen, Leslie, & Frith, 1985; Peterson, 2002). In one study, children were required to attribute beliefs to a puppet that differed from their own (Baron-Cohen et al., 1985). Only 20% of the children with Autism were able to do so, compared to 86% of children with Down syndrome and typical development. Interestingly, preschool-age children with Autism have been shown to outperform typically developing preschoolers on a particular form of theory of mind task, the false-drawing task (Peterson, 2002). In this task, children with Autism were asked to draw a red apple with a green pen. When they were finished, a green apple was placed next to the red apple and the children were then told that another child would be coming in the room and asked which apple was drawn. The children with Autism were then asked the false-belief test question, "What will he say?" One possible explanation for this superior understanding of false belief in a drawing context is that children with Autism may be able to gain early insight into mental states in relation to familiar and nonverbal activities such as drawing, even when fully developed theory of mind is absent (Peterson, 2002). Some have argued that theory of mind development in

Autism is not only delayed but is qualitatively different from the typical pattern of development. For instance, in a study of children with PDD-NOS who were given a storybook theory of mind task, the children with PDD-NOS showed specific difficulties in understanding and predicting others' emotions but were able to predict actions from beliefs and desires (Serra, Loth, van Geert, Hurkens, & Minderaa, 2002). Zelazo, Jacques, Burack, and Frye (2002) examined rule-based reasoning in conjunction with theory of mind tasks in older children and adolescents with Autism and found that, for severely impaired individuals, theory of mind performance was unrelated to rule use. However, in less severely impaired individuals, the correlation between theory of mind and rule use was high. These findings suggest that poor performance on theory of mind tasks may be related to a general difficulty in using rules to integrate two incompatible perspectives. Some researchers have proposed that theory of mind deficits are primary in Autism and at the root of the difficulties observed in social interaction and communication (Baron-Cohen et al., 1985); others argue that theory of mind abilities hinge on earlier developing social communication skills, such as joint attention (Mundy & Sigman, 1989).

Play and Language

Impairments in symbolic play, language, and communication skills are present at an early age in individuals with Autism.

Symbolic Play

Representational, or symbolic, play typically emerges between 14 and 22 months of age and includes using an object to represent another object (e.g., a block to represent a car), using absent objects as if they were present (e.g., food that does not exist), or animating objects (e.g., pretending that stuffed animals can talk; Leslie, 1987). In children with Autism, symbolic play is often absent at 18 months of age (Baron-Cohen et al., 1996) or is delayed relative to mental age-matched developmentally delayed and typical children (Charman et al., 1998; G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Mundy et al., 1987; Wing & Gould, 1979). For those children with Autism who do acquire symbolic play skills, their level of symbolic play often remains below that of their language abilities (Amato, Barrow, & Domingo, 1999; Ungerer, 1989; Wing, 1978) and is often less diverse and elaborate compared to that of developmentally delayed and typical children (Ungerer & Sigman, 1981). Further, symbolic play has been associated with both concurrent language and later social ability in young children with Autism (Sigman & Ruskin, 1999). There exists some controversy as to the cause of this impairment; some believe that it results from impairments in joint attention and understanding others, whereas others believe it hinges on deficits in symbolic thinking and executive functioning (Charman, 1997).

Language Ability

The acquisition and development of language in Autism is often delayed and/or deviant, with approximately 30% of individuals never acquiring spoken language (Bryson, 1996; Lord & Paul, 1997). This is hardly surprising given that individuals with Autism often show early impairments in symbolic play, imitation, and joint attention, which have been shown to predict language ability. In addition to delays in language acquisition, persons with Autism often exhibit atypical speech patterns, including immediate or delayed echolalia (i.e., verbatim repetition of words or phrases), unusual prosody (e.g., atypical intonation, rhythm, stress, and volume), and pronoun reversal (e.g., "*you* want a drink" instead of "*I* want a drink"), which can persist into adulthood (Cantwell, Baker, Rutter, & Mawhood, 1989; Kanner, 1943; Lee, Hobson, & Chiat, 1994).

Moreover, individuals with Autism exhibit impairments in both the pragmatic and the semantic aspects of language (Kjelgaard & Tager-Flusberg, 2001; Lord & Paul, 1997; Tager-Flusberg, 1993, 1999, 2001). Pragmatic impairments include difficulty maintaining an appropriate level of detail (e.g., often providing excessive or irrelevant details), speaking in a pedantic manner, and difficulties in reciprocity, characterized by a failure to respond to questions and comments initiated by the other person, a tendency to monopolize the conversation (generally associated with perseveration on favorite topics), and difficulties staying on topic (i.e., often inserting random and tangential comments; Capps, Kehres, & Sigman, 1998; Eales, 1993; Tager-Flusberg, 1999, 2001). Some (Eales, 1993; Tager-Flusberg, 1993, 1996) have argued that these pragmatic impairments, as well as abnormal pronoun use, are related to deficits in perspective taking (i.e., understanding another person's intentions).

Children with Autism also show impairments in how effectively they use language. In studies comparing children with Autism to children with Down syndrome matched on age and expressive language ability, children with Autism showed less variety in their use of nouns, verbs, and adjectives and used language less often to provide or elicit information (Howlin, 1984; Tager-Flusberg, 1993, 1999). Further, Kjelgaard and Tager-Flusberg (2001) found that

children with Autism who had impaired language demonstrated better vocabulary relative to higher-order language abilities, with poor performance on phonological processing and difficulties in marking tense, similar to children with specific language impairment. Finally, in their comprehension of language, children with Autism often rely on syntax as opposed to semantic content when deciphering the meaning of a sentence (Paul, Fischer, & Cohen, 1988) and often interpret what is said to them in a concrete and literal manner (e.g., "It's raining cats and dogs").

For a discussion of overlap between language impairment in Autism and specific language impairment, see the earlier section on Diagnosis.

Restricted, Repetitive Interests and Behaviors

The third symptom domain in Autism is a restricted range of behaviors, activities, and interests. Such behaviors include repetitive, stereotypic motor movements, including hand flapping, finger flicking, and complex whole-body movements, such as toe-walking and spinning, as well as persistent preoccupation with parts of objects or repetitive and nonfunctional use of objects (e.g., spinning wheels, lining things up; Campbell et al., 1990; Turner, 1999; Wing, 1988; Wing & Gould, 1979). More elaborate and complex ritualistic interests and behaviors can include precise arrangement of objects; insistence on a particular sequence of actions (i.e., compulsions); adherence to sameness in terms of routine, structure, and ordering of physical space; and intense and focused preoccupations relating to particular topics and typically involving memorization of facts (e.g., movies, camera models). Preoccupations with specific topics are often seen in high-functioning individuals (Campbell et al., 1990; Turner, 1999; Wing, 1988; Wing & Gould, 1979).

Studies that have attempted to identify the earliest emerging impairments in Autism (i.e., within the first 12 months of life) have not shown stereotypic motor movements or intense interests to be commonly present at that early age (Baron-Cohen et al., 1996; Osterling & Dawson, 1994; Robins et al., 2001). Further, young, typically developing children and children with other developmental disabilities, including mental retardation and Obsessive-Compulsive Disorder, often exhibit distress due to changes in routine and a preference for sameness (Evans et al., 1997). However, what may be specific to Autism is the number and severity of these symptoms (Charman & Swettenham, 2001).

Other Related Behaviors

The following behaviors are also common in Autism, although the number and severity of these symptoms varies across individuals.

Sensory Issues

Persons with Autism often seek sensory stimulation or have heightened negative responses to sensory stimuli. For instance, children with Autism may exhibit strong negative reactions to sounds that would not affect most individuals, such as the vacuum cleaner or noises at a distance. They may also exhibit a hypersensitivity to touch, including the feel of tags in clothing or a light embrace, while at the same time appearing insensitive to pain or showing a preference for deep pressure (e.g., tight hugs). Other children may repetitively seek out certain textures (e.g., hair, metal), touch objects to their tongue, or peer at objects out of the corner of their eyes. These sensory issues can be mild or can take up a large amount of time, interfering with family activities and/or the child's social functioning. Ornitz (1989) has argued that an impairment in the ability to modulate sensory information can lead to both under- and overreactivity to sensory stimuli.

Attention Impairments and Hyperactivity

Estimates of overactivity and/or attentional problems in Autism range from 21% to 72% (Lainhart, 1999). Children with Autism often lack attention to people and to activities that others want them to focus on, but then show overly focused attention on objects or other nonsocial stimuli. Hyperactivity in Autism appears to decrease with age but can persist into adulthood in some individuals (Kobayashi & Murata, 1998). Certain medications may improve attention and decrease hyperactivity in some children, but more controlled studies are needed (McDougle, 1998).

Self-Injurious Behaviors

Self-injurious behaviors include biting, scratching, head banging, and hair pulling and are often an expression of frustration (Donnellan, Mirenda, Mesaros, & Fassbender, 1984; Lainhart, 1999). In a recent study of 222 children with Autism under age 7, 50% demonstrated self-injurious behaviors, with as many as 15% showing severe behaviors (Baghdadli, Pascal, Grisi, & Aussilloux, 2003). Risk factors for self-injurious behaviors include lower chronological age, more severe symptoms of Autism, and more severe delays in daily living skills (Baghdadli et al., 2003). Others

have argued that these behaviors are related to level of cognitive functioning (J. Dawson, Matson, & Cherry, 1998).

Sleep and Eating Problems

Rates of sleep disturbances in Autism have been estimated to range from 11% to 65% (Chung et al., 1990; Rutter & Lockyer, 1967; Taira, Takase, & Sasaki, 1998), with average age of onset being 2 years, 3 months (Taira et al., 1998). The most common problems are difficulty falling asleep, frequent awakening, and waking early in the morning (Taira et al., 1998). Approximately 20% of adults with Autism also exhibit sleep problems (Kobayashi & Murata, 1998). However, sleep difficulties in children with Autism appear to occur at rates similar to those found in children with other psychiatric disorders (Rutter & Lockyer, 1967) and are thus not unique to Autism.

There are frequent clinical reports of restricted eating and unusual food preferences in Autism. For instance, some individuals with Autism will eat only a few foods or will eat only foods of a certain texture, color, or taste. Others exhibit rigidity at meal times, such as insisting on eating only certain brands of foods or using only certain utensils. Although eating problems can persist into adulthood, they do tend to improve as children grow older (Rutter, 1970).

ETIOLOGY

Over the past 25 years, considerable evidence has accumulated implicating genetic factors in Autism. Environmental factors and gene-environment interactions likely also contribute to the development of this disorder.

Environmental Risk Factors

Understanding environmental influences in Autism is important for several reasons. First, a better understanding of environmental factors that contribute to the disorder could help to confirm or refute reports of geographic clusters of Autism and an overall increase in rates of Autism. Second, environmental influences may help to shed light on the neurobiology of Autism. Finally, environmental factors would help to account for the high degree of heterogeneity observed in the disorder (Rodier & Hyman, 1998).

An increased rate of Autism has been reported in children who were exposed to rubella infection in the first trimester (Chess, 1977). It is likely that exposure to infectious diseases such as rubella during prenatal development may increase the risk of Autism by adding to other etiological factors, such as genetic predisposition (Rodier & Hyman, 1998). Many studies have investigated whether general suboptimal conditions (complications) during pregnancy, delivery, or infancy may contribute to Autism. No single factor has emerged consistently, and individual adverse events appear to have minimal impact (Bolton et al., 1994, 1997; Bryson et al., 1988; Gillberg & Gillberg, 1983; Levy, Zoltak, & Saelens, 1988; Lord, Mulloy, Wendelboe, & Schopler, 1991). In studies of individuals with high-functioning Autism, only one factor, a gestation period of more than 42 weeks, was found to be associated with the disorder (Lord et al., 1991). Piven et al. (1993) found that first- or fourth-born children had Autism more often than their siblings. Others have found no differences on pre- and perinatal optimality measures when comparing the births of children with Autism to those of typically developing children (Cryan, Byrne, O'Donovan, & O'Callaghan, 1996). Bolton and colleagues (1997) have concluded that optimality factors are not likely to play a direct role in Autism. Such factors are more likely related to extant fetal abnormalities, genetic factors (Bolton et al., 1994, 1997), or possibly to teratologic factors (Rodier & Hyman, 1998). Teratogenic exposure to thalidomide has been associated with Autism (Miller & Strömland, 1993). These researchers found that 5 of 15 thalidomide cases that had exposure between the 20th and 24th days of gestation had Autism, a rate of 33% during this critical period in prenatal development. Prenatal exposure to valproic acid (Moore et al., 2000; J. Williams, Whiten, Suddendorf, & Perrett, 2001) and cocaine (Davis et al., 1992) may also increase the risk of Autism.

In the late 1990s, it was proposed that a new variant of Autism caused by immunization with the combined measles, mumps, and rubella vaccine was responsible for the increase in rates of the disorder (Wakefield, 1999; Wakefield et al., 1998). These claims were made based on a sample size of 12 children with Pervasive Developmental Disorder who were referred for the evaluation of gastrointestinal diseases associated with developmental regression. A number of epidemiological studies since then have failed to confirm an association between the MMR vaccine and Autism (for reviews, see Dales, Hammer, & Smith, 2001; Farrington, Miller, & Taylor, 2001; Fombonne & Chakrabarti, 2001; Kaye, del Mar Melero-Montes, & Jick, 2001; E. N. Taylor et al., 1999; Wilson, Mills, Ross, McGowan, & Jadad, 2003). In addition, Andrews et al. (2002) have found that parents of children with Autism with regression, who were diagnosed after the publicity alleging the link between the MMR vaccine and Autism, tended to

recall onset shortly after the vaccine more often than parents of similar children who were diagnosed prior to the publicity. Thimerosal, a preservative containing ethyl mercury that is added to many vaccines, has also come under scrutiny. In 1999, the FDA determined that infants receiving multiple vaccines might be exposed to greater levels of mercury than is recommended. Although a recent review found no evidence of harm from thimerosal in vaccines (Ball, Ball, & Pratt, 2001), thimerosal-free vaccines are now available for all routine childhood immunizations (Kimmel, 2002). Several studies are currently under way examining the effects of thimerosal on childhood disorders.

Genetic Risk Factors

Next, we review what is known about genetic factors in Autism.

Single Gene Disorders

Five to 10% of Autism cases are due to an identifiable medical disorder with a known inheritance pattern, including Fragile X syndrome, untreated phenylketonuria (PKU), tuberous sclerosis, and neurofibromatosis (Szatmari, Jones, Zwaigenbaum, & MacLean, 1998). Fragile X syndrome in particular accounts for about 8% of cases of Autism (Smalley, Asarnow, & Spence, 1988).

Twin and Family Studies

A number of twin studies have provided evidence of a strong genetic component to Autism (Bailey, Le Couteur, Gottesman, & Bolton, 1995; Folstein & Rutter, 1977; Le Couteur, Bailey, & Rutter, 1989; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989). These studies have shown a higher concordance rate for Autism in monozygotic (MZ), or identical, twin pairs than in dizygotic (DZ), or fraternal, twins. In their seminal study, Folstein and Rutter reported that 36% of MZ twins were concordant for Autism, as compared to 0% of DZ twins. When they included related social or cognitive impairments, such as reading disability, language delay, articulation disorder, and mental handicap, 82% of the MZ twins and 10% of the DZ twins were concordant for Autism. A more recent study found that 60% of MZ twins were concordant for the full syndrome of Autism, and more than 90% were concordant when related social and cognitive impairments were included (Bailey et al., 1995). Heritability estimates are quite high, ranging from 91% to 93% (Bailey et al., 1995).

Family studies have provided further evidence of the heritability of Autism. The likelihood of having a second child with Autism has been estimated at 4.5% (Jorde et al., 1990, 1991), which is 45 to 90 times greater than the population risk (Cook, 1998). Further, the recurrence risk rate for siblings of females with Autism is twice that of siblings of males with Autism (Jorde et al., 1990). Recurrence risk rates following the birth of a second child with Autism range from 16% to 35% (Szatmari et al., 1998). Autism rates in second- (0.18%) and third- (0.12%) degree relatives are much lower (Szatmari et al., 1998). This sharp decrease in risk rates from first- to second- and third-degree relatives indicates that Autism is most likely the result of multiple gene (5 to 10 or more) interactions (Jorde et al., 1990; Pickles et al., 1995; Risch et al., 1999).

Broader Autism Phenotype

A broader Autism phenotype, or "lesser variant" of Autism, is defined as having one or more difficulties in social functioning, communication, cognition, and interests/behaviors (Baron-Cohen & Hammer, 1997). Broader phenotype studies have been on the rise in recent years and have examined characteristics of first-, second-, and third-degree relatives of individuals with Autism. As many as 10% to 25% of siblings who do not meet criteria for Autism demonstrate broader phenotype impairments, including learning difficulties, language and communication deficits, and social impairments (Bolton et al., 1994; Bolton & Rutter, 1990). A more recent study reported that 12% of siblings and 10% of parents exhibited broader phenotype characteristics (Starr et al., 2001).

Parents of children with Autism were 3 times as likely as parents of children with Down syndrome to have had definite or probable language problems in childhood, including articulation deficits, trouble learning to read, or trouble with spelling, and showed a significant split between verbal and performance IQ scores relative to controls (Folstein et al., 1999). A study of personality traits in first-degree relatives found that relatives of individuals with Autism were more anxious, impulsive, aloof, shy, sensitive, irritable, and eccentric than relatives of individuals with Down syndrome (Murphy et al., 2000). In this same study, three factors were derived for the Autism group: withdrawn, difficult, and tense. The authors concluded that the withdrawn and difficult factors appeared to reflect social functioning impairments, whereas the tense factor appeared to be related to the burden of raising a child with Autism. In multiplex families (i.e., those with two or more children with Autism), parents of children with high rates of repetitive behaviors showed significantly more obsessive-compulsive traits and were more likely to have Obsessive-Compulsive

Disorder than parents of children with low repetitive behavior scores (Hollander, King, Delaney, Smith, & Silverman, 2003). Still other studies have reported increased rates of pragmatic language impairments (Landa et al., 1992) and executive function deficits (e.g., set shifting and planning; Hughes, Plumet, & Leboyer, 1999) and difficulties in reading comprehension and rapid automatized naming (Piven & Palmer, 1997) in family members.

In second- and third-degree relatives, Szatmari et al. (2000) found that 10% demonstrated communication impairments, 7% exhibited repetitive activities, 14% showed social impairments, 23% met criteria for the "broad" definition of the lesser variant, and 7% met criteria for the "narrow" definition of the lesser variant, as defined by Bolton et al. (1994).

Like Autism, broader phenotype characteristics are much more common in males than females, although this is less true of the mildest cases, and are usually evident in early childhood (Bailey, Phillips, & Rutter, 1996). However, unlike Autism, individuals with broader phenotype characteristics are generally of normal intelligence, and no association with epilepsy has been found (Bailey et al., 1996). Some researchers have proposed that the broader phenotype is simply a lower dose of the genetic predisposition to Autism, whereas others argue a "two-hit" mechanism. In this view, one set of factors predisposes the individual to the broader phenotype, and a separate set of factors is involved in the development of Autism (Bailey et al., 1996). In any case, these findings in the broader phenotype literature suggest that incorporating quantitative measures of autistic traits that may be expressed to a lesser degree in relatives may be useful in studies of the genetic basis of Autism.

Sibling Linkage and Quantitative Trait Locus Analyses

Sibling linkage studies use highly variable polymorphisms spaced evenly throughout the genome to identify chromosome regions that are shared among siblings with Autism. Thus far, findings from Autism linkage studies have been inconsistent. Possible susceptibility regions include chromosomes 1p, 2q, 7q, 13q, 16p, and 19q (Alarcon, Cantor, Liu, & Gilliam, 2002; Ashley-Koch et al., 1999; Bailey et al., 1998; Barrett et al., 1999; Bradford et al., 2001; Buxbaum et al., 2001; International Molecular Genetic Study of Autism Consortium, 1998, 2001; Liu, 2001; Philippe et al., 1999; Risch et al., 1999). Only regions 2q and 7q have been implicated in more than one study, with chromosome 7 appearing the most promising (Ashley-Koch et al., 1999; Barrett et al., 1999; Collaborative Linkage Study of Autism, 2001). Chromosome 7 has been linked both to Autism and to language disorders, such as specific language impairment (Folstein & Mankoski, 2000; Warburton et al., 2000). In addition, the 7q31 region contains other genes of interest, including the serotonin receptor gene and the reelin gene (see section on Candidate Gene Studies).

Quantitative trait loci (QTL) refer to genetic loci that modify the expression of a phenotypic trait in a continuous rather than categorical way. In a study of multiplex families that included parent and proband language phenotypes, Bradford et al. (2001) found that the highest signals, on chromosome 7q and 13q, were primarily accounted for by families in which both probands exhibited language delay. Similarly, a nonparametric multipoint linkage analysis of 152 families from the Autism Genetic Resource Exchange that included QTL from the Autism Diagnostic Interview ("age at first word," "age at first phrase," and a composite of "repetitive and stereotyped behavior") revealed the most robust QTL results for "age at first word" on chromosome 7q (Alarcon et al., 2002).

Autism and Specific Language Impairment

Both Autism and SLI are highly heritable, complex genetic disorders (Santangelo & Folstein, 1999; Tallal & Benasich, 2002; Tomblin & Zhang, 1999) that involve several genes. In addition, family studies have distinguished a broader phenotype. In family members of persons with Autism, elevated rates of language-related impairments have been found, including language delay and language-related learning deficits (Bolton et al., 1994; Fombonne et al., 1997; Piven & Palmer, 1997). Among siblings of persons with SLI, there is an elevated risk of Autism (Tomblin, Hafeman, & O'Brien, 2003). In addition, genetic studies have reported linkage to the same region on chromosome 7 for both disorders (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; International Molecular Genetic Study of Autism Consortium, 1998). Therefore, it is possible that families with SLI and Autism share some of the same genetic and phenotypic characteristics. Future research that targets the subgroup of children with Autism who exhibit those aspects of language impairment that are also characteristic of SLI may be useful in defining the genetic phenotype of Autism.

Candidate Gene Studies

Numerous candidate gene studies in Autism have been conducted, with little success thus far. Here, a few of such studies are reviewed.

Increased blood and urinary serotonin levels and the positive effect of selective serotonin reuptake inhibitors (SSRIs) on some symptoms of Autism (see Intervention

section later in this chapter) led to studies of genes involved in the serotonin system. Although initial studies implicated the serotonin transporter gene (Cook et al., 1997), later studies did not confirm a link (Klauck, Poustka, Benner, Lesch, & Poustka, 1997; Maestrini et al., 1999; Persico et al., 2000; Zhong et al., 1999).

Rodier, Ingram, Tisdale, Nelson, and Romano (1996) conducted an autopsy study to examine the motor nuclei in the brain stem of an individual with Autism. They found shortening of the brain stem between the trapezoid body and the inferior olive, and near-complete absence of the facial nucleus and superior olive, abnormalities similar to those reported in HoxA-1 gene knock-out mice. The HoxA and HoxD genes have also been shown to influence differentiation of the fingers and toes. One trait, the relative length of the second and fourth digits, has been found to correlate with Autism (Manning, Callow, & Bundred, 2003). These findings suggest that the Hox genes may be implicated in Autism. However, other studies have reported conflicted findings regarding an association between the HoxA-1 gene and Autism (B. Devlin et al., 2002; Gallagher, Hawi, Kearney, Fitzgerald, & Gill, 2004; Ingram et al., 2000; Li et al., 2002).

Reelin is an important secretory glycoprotein that regulates normal layering of the brain, normal cell signaling, correct axonal growth, synaptic plasticity, and programmed cell death (Adams & Cory, 1998; Fatemi, Stary, Halt, & Realmuto, 2001; Ogawa et al., 1995). Fatemi and colleagues found a decrease in the level of reelin in the autistic cerebellum, which may be responsible for some of the cognitive deficits in Autism. In another study by these same researchers (Fatemi, Stary, & Egan, 2002), a reelin 410 deficiency was observed in autistic twins and their first-degree relatives (mothers, fathers, and typically developing siblings). A genetic study of affected sib pairs did not provide support for the reelin gene as a susceptibility gene in Autism, but a family-based association study using data from the Autism Diagnostic Interview-Revised found that children with at least one large reelin gene allele (> 11 repeats) tended to have earlier onset of phrase speech (Zhang et al., 2002). Therefore, the reelin gene may play a role in the etiology of some cases of Autism. However, it should be noted that reelin has also been implicated in Schizophrenia (Fatemi, Earle, & McMenomy, 2000; Guidotti et al., 2000; Impagnatiello et al., 1998), Bipolar Disorder (Fatemi et al., 2000; Guidotti et al., 2000), Major Depression (Fatemi et al., 2000), and possibly Schizoaffective Disorder (Fatemi, Stary, & Egan, 2002). Furthermore, a more recent study found no evidence for a link between reelin and Autism (G. Devlin et al., 2004).

Future Directions

Over the past 25 years, we have achieved a deeper understanding of the genetic and environmental risk factors involved in the development of Autism. Regarding the study of genetic factors in particular, we now know that Autism cannot be attributed to a single gene, but rather, to multiple gene interactions. Each gene acts as a risk factor for an element of this complex disorder, with the greatest risk resulting from a large number of genes acting in concert. Recent research also suggests that Autism susceptibility genes may produce effects on a phenotypic continuum. Given this possibility, future research will incorporate the use of dimensional measures—behavioral and/or biological—of core Autism traits to aid in the identification of the specific genes involved in this disorder.

BRAIN FUNCTIONING AND DEVELOPMENT IN AUTISM

It is believed that the brain regions affected in Autism are disrupted early in development, very likely during the prenatal period. Brain regions hypothesized to be affected include the cerebellum, temporal lobe areas (e.g., medial temporal lobe, fusiform gyrus, superior temporal sulcus), the prefrontal cortex (both ventromedial and dorsolateral prefrontal cortex and Broca's area), and the inferior parietal cortex (Bachevelier, 1994; Baron-Cohen et al., 2000; Bauman & Kemper, 1994; Courchesne, 1989; G. Dawson, Webb, et al., 2002).

Enlarged Cerebral Volume

Increased cerebral volume is one of the earliest abnormalities in brain development apparent in children with Autism (Bailey et al., 1998; Piven, Harper, et al., 1995, 1996; Sparks et al., 2002). In a recent study by Courchesne and colleagues (Courchesne, Carper, & Akshoomoff, 2003), it was found that head circumference at birth in infants later diagnosed with Autism Spectrum Disorder was significantly smaller than that found in typically developing infants; however, between 1 to 2 months of age and 6 to 14 months of age, there was an abnormally accelerated rate of growth in head circumference in infants with ASD, more so for those with Autistic Disorder as compared to PDD-NOS. These results suggest that increased brain volume may be an early indicator of Autism, preceding the behavioral onset of the disorder (Courchesne et al., 2003). Further, Aylward, Minshew, Field, Sparks, and Singh (2002) found

that children with Autism age 12 years and younger had significantly larger brain volumes than controls; however, brain volumes for individuals with Autism over 12 years of age did not differ from controls, suggesting that there is a slight decrease in brain volume beginning in adolescence in children with Autism at the same time that typically developing children are experiencing a slight increase in volume. Although other studies have also shown brain enlargement in younger children with Autism, but not in older children or adults with Autism (Akshoomoff, Pierce, & Courchesne, 2002; Courchesne, Bartholomeusz, Karns, & Townsend, in press; Courchesne et al., 2001), brain enlargement has also been observed in older individuals with Autism through postmortem and imaging studies; thus, within individuals, the course of brain development may vary (Bailey et al., 1998; Bauman & Kemper, 1985; Courchesne, Muller, & Saitoh, 1999; Lainhart et al., 1997; Piven, Harper, et al., 1995; Piven et al., 1996).

Cerebellum

Neuropathological studies have found reduced numbers of Purkinje or granule cells in the cerebellum (Bailey et al., 1998; Bauman & Kemper, 1994; Raymond, Bauman, & Kemper, 1996). Courchesne (1989) has argued that loss of Purkinje cells may disrupt normal cerebellar functioning necessary for rapid shifts of attention, motor behaviors, and associative learning, and may lead to excitatory interference to brain stem and thalamic systems, which mediate attention and arousal. Early impairments in the cerebellum may also affect later development of limbic regions (Courchesne, Chisum, & Townsend, 1994).

Medial Temporal Lobe

Based on MRI of 3- to 4-year-old children with Autism Spectrum Disorder compared to those with developmental delay or typical development, Sparks et al. (2002) reported that amygdala enlargement exceeded that of overall increased cerebral volume and was related to more severe joint attention and face recognition impairments (Howard et al., 2000; Sparks et al., 2002). Right amygdala enlargement was found to predict a slower rate of growth in social and language skills between ages 3 to 4 years and 6 to 7 years for children with Autistic Disorder (Munson et al., 2004). Taken together, these findings suggest that early increased amygdala volume may be a marker of severity of Autism impairment.

Autopsy studies have revealed abnormalities of the medial temporal lobe (MTL), including the amygdala, hippocampus, and surrounding regions (Bauman & Kemper, 1994). Young children with Autism perform poorly on MTL tasks, including visual recognition memory (paired comparison, delayed nonmatched to sample) and deferred imitation tasks (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; G. Dawson, Munson, et al., 2002). It has been hypothesized that Autism might involve an impairment in other aspects of hippocampal functioning as well, such as feature binding (i.e., binding of items or events into a cohesive memory), context memory, and source memory (G. Dawson, Webb, et al., 2002). Such memory functions are important in representing social events (see H. Cohen et al., 1999; N. Cohen & Eichenbaum, 1993). An impairment in feature binding, that is, a failure to integrate information into a meaningful whole (Mottron, Belleville, & Menard, 1999; Shah & Frith, 1993), has also been demonstrated in parents of children with Autism (Happe, Briskman, & Frith, 2001) and may explain the difficulties in face processing found in Autism.

A number of studies have shown that the MTL is involved in social perception (Bachevalier, 2000; Baron-Cohen et al., 2000; G. Dawson, 1996), including recognition of faces and facial expressions (Aggleton, 1992; Jacobson, 1986; Nelson & deHaan, 1996), forming associations between stimuli and reward value (Baxter & Murray, 2000; Gaffan, 1992; Malkova, Gaffan, & Murray, 1997), recognizing the affective significance of stimuli (LeDoux, 1987), perceiving body movements, such as gaze direction (Brothers, Ring, & Kling, 1990), and certain cognitive abilities that may be important for social perception and imitation (Murray & Mishkin, 1985).

In a study by G. Dawson and colleagues (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998), MTL and prefrontal function in school-age children with Autism was assessed by using the delayed nonmatch to sample (DNMS) and delayed response tasks, respectively. They found that children with Autism were impaired on the DNMS task and the delayed response task compared to mental age-matched children with developmental delays and typical development. Severity of Autism symptoms correlated strongly with DNMS performance, but not with performance on the delayed response task. To extend this study, a more comprehensive set of neuropsychological tasks was administered to a younger and larger sample of children with Autism (G. Dawson, Munson, et al., 2002). The test battery included three tasks measuring dorsolateral prefrontal function and three tasks assessing MTL and/or MTL-

ventromedial prefrontal function. Interest in ventromedial prefrontal function was based on findings that patients with ventromedial prefrontal lesions also exhibited deficits in social cognition and theory of mind (Cicerone & Tanenbaum, 1997; Damasio, Tranel, & Damasio, 1990; V. E. Stone, Baron-Cohen, & Knight, 1998). Furthermore, fMRI studies have shown ventromedial prefrontal activation during theory of mind and social attribution tasks (Fletcher et al., 1995; Happe et al., 1996; Schultz, Romanski, & Tsatsanis, 2002).

G. Dawson, Munson, et al. (2002) examined the relationship between performance on the neuropsychological tasks and a core Autism symptom, joint attention. Results showed that the children with Autism were significantly impaired in joint attention ability compared to controls and that performance on the MTL-ventromedial prefrontal tasks was more strongly related to joint attention ability than performance on the dorsolateral prefrontal tasks. These findings suggest that core Autism symptoms, such as joint attention ability, may be related to dysfunction of the MTL-ventromedial prefrontal circuit.

A number of investigators have suggested that the severity or extent of MTL dysfunction varies across individuals with Autism and may account for the variability in functioning (Bachevalier, 1994; Barth, Fein, & Waterhouse, 1995; G. Dawson, 1996; Waterhouse, Fein, & Modahl, 1996). This idea is based on the work of Bachevalier, who found that monkeys with both hippocampal and amygdala lesions exhibited more severe memory and social impairments than monkeys with amygdala lesions alone. In individuals with Autism, memory impairments related to MTL function were found only in lower-functioning individuals (Ameli, Courchesne, Lincoln, Kaufman, & Grillon, 1988; Barth et al., 1995; Boucher, 1981; Boucher & Warrington, 1976; Rumsey & Hamburger, 1988). G. Dawson and colleagues (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998) found that children with Autism who performed fewer immediate and deferred imitative acts (hippocampal system) also required more trials to reach criterion on the DNMS, an MTL task, and exhibited more severe symptoms of Autism, such as greater joint attention impairments.

A variation on this hypothesis posits that individuals with less severe symptoms are impaired in the temporal-parietal association regions and the parietal cortex but have little or no MTL dysfunction, whereas individuals with more severe symptoms have significant MTL dysfunction that then leads to prefrontal impairments (Waterhouse et al., 1996). In this view, prefrontal impairments are the downstream consequence of faulty MTL functioning. In support of this hypothesis, studies with monkeys have shown that early MTL damage disrupts prefrontal cortex development (Bertolino et al., 1997; Chlan-Fourney, Webster, Felleman, & Bachevalier, 2000; Saunders, Kolachana, Bachevalier, & Weinberger, 1998). In studies of very young children with Autism (age 3 to 4), no differences in prefrontal performance were found relative to mental age-matched controls (G. Dawson, Munson, et al., 2002; Griffith, Pennington, Wehner, & Rogers, 1999). However, older elementary school-age children with Autism have demonstrated prefrontal (executive function) deficits compared to controls (G. Dawson, Meltzoff, Osterling, & Rinaldi, 1998; McEvoy, Rogers, & Pennington, 1993; Pennington & Ozonoff, 1996). These results are not surprising given that executive function ability is just emerging during the preschool period (Diamond & Goldman-Rakic, 1989). Longitudinal studies of executive function in younger, and also in more severely affected, individuals with Autism are needed to better understand the course of prefrontal dysfunction in Autism.

Abnormalities in Brain Regions Involved in Face Processing

Studies have shown that individuals with Autism are impaired in their ability to recognize and match faces (Boucher & Lewis, 1992; Boucher et al., 1998; Cipolotti et al., 1999; Hauck et al., 1998; Jambaque et al., 1998; Klin et al., 1999; Ozonoff et al., 1990; Tantam et al., 1989; Teunisse & DeGelder, 1994) and use atypical strategies for processing faces (Hobson et al., 1988; Joseph, 2001; Klin et al., 2002; Langdell, 1978). For typical individuals, the most salient parts of the face are, in order of importance, eyes, mouth, and nose (Shepherd, 1981). Individuals with Autism, however, spend more time looking at the lower half of the face rather than the eyes and are better at matching faces when matching is based on the lower half of the face as opposed to the upper face or eyes (Joseph, 2001; Langdell, 1978). Further, Klin and colleagues (2002) used eye-tracking technology to demonstrate that when viewing emotional and dramatic scenes from a movie, adults with Autism spent more time looking at mouths, bodies, and objects than eyes.

Functional MRI studies in Autism show no activation of the fusiform gyrus, a brain area specialized for face processing (Pierce, Muller, Ampbrose, Allen, & Courchesne, 2001; Schultz et al., 2000), and increased activation in the frontotemporal regions, but not the amygdala, when making inferences from the eyes (Baron-Cohen, Scahill, et al.,

1999). Electrophysiological studies also have demonstrated face processing abnormalities. As mentioned in the section on Symptom Presentation, G. Dawson and colleagues (G. Dawson, Carver, et al., 2002) found that 3- to 4-year-old children with Autism failed to show differential ERPs to faces, whereas they showed normal ERPs to objects. A study of ERPs in adolescents and adults with Autism demonstrated that these individuals have slower processing of faces, fail to show a processing speed advantage for faces relative to nonface stimuli, and have atypical lateralization of ERPs to faces (McPartland et al., 2001a, 2001b).

It is possible that abnormal face processing in Autism is related to an innate abnormality in face processing regions, such as the fusiform face area and superior temporal sulcus. This would result in impairments in early stage face processing (faulty "starter set" for encoding). Alternatively, face processing impairments might be secondary to an impairment in social motivation/sensitivity to social reward. Specifically, an impairment in social motivation might result in reduced attention to faces and facial expressions. This might further lead to a failure to develop expertise in face processing (Carver & Dawson, 2002; G. Dawson, Ashman, & Carver, 2000; Dawson & Zanolli, 2003; Grelotti, Gauthier, & Schultz, 2002; Mundy & Neal, 2001). If the latter explanation is correct, then early intervention might be expected to have a significant impact on face processing development. Early intervention approaches often focus on rewarding children for looking at others and making eye contact (G. Dawson & Zanolli, 2003). Current studies are examining the impact of such early interventions on the development of face processing in children with Autism.

Brain Regions Involved in Motor Imitation

Motor imitation impairments are well documented in Autism (G. Dawson & Adams, 1984; G. Dawson & Lewy, 1989; DeMyer et al., 1972; Meltzoff & Gopnik, 1993; Rogers, 1999; Rogers & Pennington, 1991; I. M. Smith & Bryson, 1994; J. Williams et al., 2001) and may be a precursor to the development of theory of mind (Meltzoff & Gopnik, 1993). A number of brain regions are involved in imitation. For example, patients with left frontal lesions display dyspraxia (Goldenberg, 1995; Goldenberg & Hagman, 1997; Merians et al., 1997); the left hemisphere is activated during imitation of hand and facial movements (G. Dawson, Warrenburg, & Fuller, 1985), and, in animals, cells in the superior temporal sulcus code the movements of the face, limbs, and whole body (Oram & Perrett, 1994; Perrett et al., 1984, 1985, 1989). In the prefrontal cortex in monkeys, "mirror neurons" fire when a monkey performs or views another monkey performing certain actions (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Matelli, et al., 1996). Other brain areas that are important in motor imitation include the parietal and prefrontal regions (premotor cortex and Broca's area; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996) and the superior temporal gyrus (Decety, Chaminade, Grezes, & Meltzoff, 2002). Thus far, few, if any, functional brain imaging studies have examined patterns of brain activation during imitation in Autism; this is an area ripe for study.

Brain Regions Involved in Language

As described in the sections on Diagnosis and Etiology, some have argued that there is overlap between Autism and specific language impairment, with a subgroup of individuals with Autism showing the characteristic profile of SLI (Kjelgaard & Tager-Flusberg, 2001; Tager-Flusberg, 2003, in press; Tager-Flusberg & Joseph, 2003). MRI findings have shown that this subgroup of children with Autism has the same neurocognitive phenotype as children with SLI. Other studies of SLI have reported volumetric and asymmetry differences in the planum temporale and parietal and frontal cortex, as well as alterations in the magnocellular neurons in the lateral geniculate nucleus and medial geniculate nucleus (see Tallal & Benasich, 2002). Positron emission tomography (PET) studies of phonological processing have most consistently activated Broca's area (Demonet et al., 1992; Paulescu, Frith, & Frackowiak, 1993; Zatorre, Evans, Meyer, & Gjedde, 1992), the secondary auditory cortex (Demonet et al., 1992; Paulescu et al., 1993; Sergent, Zuck, Levesque, & MacDonald, 1992), and the supramarginal gyrus (Paulescu et al., 1993; Petersen, Fox, Posner, Mintun, & Raichle, 1989; Zatorre et al., 1992).

A phonological processing impairment in 3- to 4-year-old children with Autism was found in a study of speech processing using an electrophysiological mismatch negativity (MMN) paradigm (Coffey-Corina & Kuhl, 2001). In this study, the children watched a video of their choice while passively listening to two different speech sounds: One syllable, /wa/, was presented on 85% of the trials (standard), and a different syllable, /ba/, was presented on the remaining 15% of trials (deviant). Results indicated that whereas typically developing children showed a significant difference between standards and deviants, children with Autism showed no significant difference for the two

types of speech stimuli. Therefore, in some children with Autism, basic auditory-linguistic processing may be fundamentally different.

Summary

In summary, Autism involves dysfunction of multiple brain regions. Our understanding of the neural bases of Autism has increased as a result of both structural and functional brain imaging studies, many of which have only recently included younger children. Additional research, particularly longitudinal studies of brain function in individuals with Autism, is needed to better understand the complex course of brain development and function in this disorder.

NEUROCHEMICAL FINDINGS AND PHARMACOLOGICAL INTERVENTIONS

Findings from a number of studies suggest that neurochemical factors play a major role in Autism (Tsai, 1999). Studies that have examined neurotransmitters in individuals with Autism are reviewed next.

Serotonin

Serotonin is a neurotransmitter that affects a range of behaviors and processes, including sleep, appetite, learning, memory, pain and sensory perception, motor function, and early brain development and plasticity (Azmitia & Whitaker-Azmitia, 1997; Lauder, 1993; Volkmar & Anderson, 1989). Hyperserotonemia (i.e., having peripheral serotonin levels in the upper 5% of the normal distribution) has been consistently reported in about one-third of persons with Autism, with mean levels ranging from 17% 128% higher than controls (G. M. Anderson et al., 1987; G. M. Anderson, Horne, Chatterjee, & Cohen, 1990; G. M. Anderson & Hoshino, 1987; Cook et al., 1993; Herault et al., 1996; Piven et al., 1991). Using PET technology, researchers have been able to examine serotonin more directly. For instance, in a study of seven boys with Autism, a pattern of increased synthesis of serotonin in the contralateral dentate nucleus of the cerebellum and decreased synthesis of serotonin in the thalamus and frontal cortex was observed (Chugani et al., 1997). Interestingly, elevated levels of serotonin have also been observed in roughly 50% of mothers and fathers and in 87% of siblings of persons with Autism (Leboyer et al., 1999).

Dopamine

Most studies of dopamine in Autism have focused on homovanillic acid (HVA), the main metabolite of dopamine. Although results have not been consistent, some studies have found elevated HVA levels in children with Autism (Gillberg & Svennerholm, 1987). In another study, elevated HVA levels were found in more severely impaired children, especially those with more severe stereotypic and repetitive motor behaviors (Narayan, Srinath, Anderson, & Meundi, 1993). Dopamine agonists, such as stimulants, have been shown to increase stereotypies, aggression, and hyperactivity in children with Autism (Young, Kavanagh, Anderson, Shaywitz, & Cohen, 1982), which suggests that the dopamine system is involved in this disorder.

Epinephrine and Norepinephrine

Epinephrine and norepinephrine impact memory, attention, arousal, movement, anxiety, and respiratory and cardiac function (Volkmar & Anderson, 1989). Researchers have investigated the idea that increased levels of norepinephrine (a neurotransmitter and hormone) may influence symptoms of arousal and anxiety in individuals with Autism. A number of studies have found no differences between Autism subjects and controls in cerebral spinal fluid, plasma, and urinary excretion of norepinephrine's principal metabolite, 3-methoxy-4-hydroxyphenyleneglycol, or in urinary excretion rates of epinephrine, norepinephrine, and vanillylmandelic acid (Gillberg, Svennerholm, & Hamilton-Hellberg, 1983; Minderaa, Anderson, Volkmar, Akkerhuis, & Cohen, 1994; Young et al., 1982). In one study, however, both epinephrine and norepinephrine were significantly lower in the Autism group than in controls (Launay et al., 1987).

Endogenous Opioids

Endogenous opioid peptides, or endorphins, have been linked to social behaviors, emotion, motor activity, and pain perception (Panksepp & Sahley, 1987). Some researchers have suggested that elevated opioids may play a role in the self-injurious behaviors and cognitive and socioemotional deficits observed in Autism (Panksepp, 1979; Panksepp & Sahley, 1987). Thus far, however, results have been inconsistent, with some reporting increased levels of opioids (Tordjman et al., 1997) and others reporting decreased levels of endorphins in Autism (Leboyer et al., 1994; Sandman, Barron, Chicz-DeMet, & DeMet, 1990).

Pharmacological Treatments

Most of the pharmacological studies to date have been open trial (rather than controlled) studies with very small sample sizes. Nevertheless, a number of drugs have been shown to be promising in ameliorating certain symptoms of Autism. Most of these drugs target related symptoms, such as hyperactivity and self-injurious behavior, but some (e.g., SSRIs) have recently been shown to improve core social symptoms of Autism.

Serotonergic Drugs

Two groups of medications that influence the serotonin system—antidepressants and antianxiety drugs—have been studied in Autism.

SSRIs and Other Antidepressants. Medications that influence serotonin include clomipramine, fluoxetine (Prozac), fluvoxamine, and sertraline. Extant evidence suggests that these drugs may reduce hyperactivity in children with Autism (Gordon, Rapoport, Hamburger, State, & Mannheim, 1992; Gordon, State, Nelson, Hamburger, & Rapoport, 1993) and improve obsessive-compulsive symptoms, social withdrawal, reciprocal social interaction, motor stereotypies, aggression, and self-injurious behaviors (Gordon et al., 1993; Harvey & Cooray, 1995; Hellings, Kelley, Gabrielli, Kilgore, & Shah, 1996; McDougle, Price, & Goodman, 1990; Potenza & McDougle, 1997; Steingard, Zimnitzky, DeMaso, Bauman, & Bucci, 1997). However, use of these drugs can lead to serious cardiovascular side effects and lowered seizure thresholds and should therefore be prescribed with caution.

Antianxiety Drugs. In two studies of buspirone, reductions in hyperactivity were noted (McCormick, 1997; Realmuto, August, & Garfinkel, 1989). More research needs to be done on the efficacy of antianxiety drugs in treating symptoms of Autism.

Dopaminergic Drugs

Antipsychotics, including haloperidol, risperidone, and clozapine, have all been shown to produce at least moderate reductions in symptoms of hyperactivity, but effects are less clear on symptoms of impulsivity and inattention (L. T. Anderson & Campbell, 1989; L. T. Anderson et al., 1984; Campbell et al., 1978; Fisman & Steele, 1996; Horrigan & Barnhill, 1997; Joshi, Capozzoli, & Coyle, 1988; Malek-Ahmadi & Simonds, 1998; McDougle et al., 1997; Nicolson, Awad, & Sloman, 1998; Perry, Pataki, Munoz-Silva, Armenteros, & Silva, 1997; Potenza, Holmes, Kanes, & McDougle, 1999; Zuddas, Ledda, Fratta, Muglia, & Cianchetti, 1996). Risperidone and clozapine are both dopamine and serotonin receptor antagonists.

Epinephrine- and Norepinephrine-Related Drugs

Clonidine is an adrenergic receptor agonist that decreases norepinephrine neurotransmission (Tsai, 1999). There is modest evidence that clonidine may reduce symptoms of hyperactivity in children with Autism (Frankhauser, Karumanchi, German, Yates, & Karumanchi, 1992; Jaselskis, Cook, Fletcher, & Leventhal, 1992). The use of clonidine for managing hyperactivity and sleep problems in children with Autism has escalated in recent years, although the empirical data supporting its efficacy are scanty. Desipramine is a selective norepinephrine uptake inhibitor that has been shown to reduce hyperactivity in children with Autism (Gordon et al., 1992).

Psychostimulants

Again, very few studies have been done to assess the effects of psychostimulants, such as Ritalin and d-amphetamine. However, initial results suggest that these drugs may be helpful in improving attention and social responsiveness (Vitriol & Farber, 1981), irritability (Quintana et al., 1995), and hyperactivity (Geller, Guttmacher, & Bleeg, 1981; Handen, Johnson, & Lubetsky, 2000). Other studies have shown deleterious effects following the use of stimulants in patients with pervasive developmental disorders, including overactivity and stereotypical behavior (Schmidt, 1982), fearfulness, separation anxiety, and increased hyperactivity (Realmuto et al., 1989), and agitation, aggression, and motor and phonic tics (Volkmar, Hoder, & Cohen, 1985).

Opiate Agonists

Naltrexone has been shown to reduce hyperactivity in individuals with Autism (Campbell et al., 1993; Campbell, Overall, Small, & Sokol, 1989; Kolmen, Feldman, Handen, & Janosky, 1995, 1997; Willemsen-Swinkels, Buitelaar, Nijhof, & Van Engeland, 1995; Willemsen-Swinkels, Buitelaar, & Van Engeland, 1996). Opiate blockers may also reduce self-injurious behaviors (Werry & Aman, 1999).

Vitamin and Diet Therapies

It should be noted that rigorous empirical studies of the efficacy of vitamin and dietary treatments for Autism are lacking. Nevertheless, there has been some evidence for metabolic abnormalities, including high or low excretion of uric acid (Coleman & Gillberg, 1993; Lis, McLaughlin, Lis, & Stubbs, 1976), high excretion of hippuric acid (Lis

et al., 1976), low urinary tyrosine (Visconti et al., 1994), and excretion of peptides (Kniusberg, Wiig, Lind, Nogland, & Reichelt, 1990; Reichelt, Kniusberg, Nodland, & Lind, 1994), related to gut symptomatology (i.e., "leaky gut") in some individuals with Autism. A few studies have examined vitamin and dietary therapies to address metabolic abnormalities. For instance, pyridoxine (vitamin B_6) has been reported to improve social behavior and language, increase interest in the environment, and reduce aggression in subjects with Autism (Coleman, 1989; Kleijnen & Knipschild, 1991; Lelord, Barthelemy, & Martineau, 1988). Folic acid has been reported to decrease hyperactivity and increase attention and social behavior in subjects with Autism with Fragile X syndrome (Coleman, 1989). The diet most often associated with the treatment of Autism is the low-casein and/or low-gluten diet (Kniusberg et al., 1990). This diet is purported to improve symptoms of Autism by removing proteins that produce toxic peptides. A diet low in casein and gluten was reported to increase social interaction, improve language, and increase interest in the environment after 1 year (Kniusberg et al., 1990). More research on dietary intervention is clearly needed.

PSYCHOSOCIAL INTERVENTIONS

A number of psychosocial treatments are available for individuals with Autism. These treatments target skill domains that are typically impaired in Autism, including social, cognitive, language, and behavioral functioning. Regardless of the treatment approach, it is important that intervention begin at an early age for the best prognosis.

Early Intervention

Early social and language input is critical for normal brain and behavioral development (Mundy & Neal, 2001; Rogers, 1998). If Autism can be identified early and intervention can begin during the first few sensitive years of life, there is the greatest potential for having a significant impact on the developing nervous system and improved social and behavioral outcomes for children with Autism (G. Dawson, Ashman, et al., 2000; Rogers, 1998).

Several studies suggest that early intervention can result in dramatic improvements in some children with Autism (Birnbrauer & Leach, 1993; G. Dawson & Osterling, 1997; Fenske, Zalenski, Krants, & McClannahand, 1985; Harris, Handleman, Gordon, Kristoff, & Fuentes, 1991; Lovaas, 1987; McEachin et al., 1993; Rogers, 1998; Sheinkopf & Siegel, 1998). As summarized by G. Dawson and Osterling, Green, Brennan, and Fein (2002), Rogers, and the National Research Council (2001), although intervention approaches have varied across different outcome studies, most have several features in common:

1. A focus on the curriculum domains of attention, imitation, language, toy play, and social interaction;
2. Programs that incorporate developmental sequence;
3. Teaching strategies that offer a high level of support for the child, many of which rely on principles of applied behavioral analysis (see later discussion);
4. Specific strategies focused on reducing interfering /problem behaviors;
5. A high level of involvement of parents;
6. Careful transitioning from one-to-one teaching to small groups;
7. Highly trained staff;
8. High levels of supervision of therapists;
9. Intensive intervention consisting of about 25 hours a week of structured intervention lasting for at least 2 years; and
10. Onset of intervention by 2 to 4 years.

When these features are present, results have been impressive for a subgroup of children, including robust gains in IQ, language, and educational placement (G. Dawson & Osterling, 1997; Rogers, 1998). There is evidence that very early intervention, by 2 to 3 years of age, results in more positive outcomes than intervention that begins later (Simeonsson, Olley, & Rosenthal, 1987).

There is some debate as to the optimal number of hours of early intervention. Lovaas's (1987) original study advocated 40 hours per week of one-on-one behavioral intervention during the preschool period. The National Research Council (2001) currently recommends at least 25 hours of structured intervention for children with Autism, with a strong emphasis on one-on-one intervention, which can include specialized education, speech and language therapy, occupational therapy, applied behavioral analysis, and other services that promote the child's communication and social development.

To date, most studies on the effectiveness of early intervention have had significant methodological limitations (for reviews, see G. Dawson & Osterling, 1997; Rogers, 1998; T. Smith, 1999). Lovaas's (1987) original study showing positive effects of early intervention, although important and provocative, had methodological limitations with respect to choice of outcome measures, selection bias, and representativeness of sample (Gresham & MacMillan, 1998). In a randomized study, T. Smith,

Groen, and Wynn (2000) compared a group of 15 children receiving "intensive intervention" consisting of an average of 24 hours of early intervention weekly (with reduction in hours after year 1) to a group of 13 children whose parents were taught to use early intervention techniques for 5 hours per week over a 3- to 9-month period, with consultation every 3 months thereafter. Children began treatment at about age 3 and were seen at follow-up at about age 7 to 8. At follow-up, the intensive treatment group had a statistically significant advantage over the parent training group in IQ, visual-spatial skills, and language development, but not adaptive behavior. Within the intensively treated group, children with a diagnosis of PDD-NOS obtained higher outcome scores than those with a diagnosis of Autism, although these differences were not statistically significant. In both groups, large individual differences in response were apparent. In the intensive treatment group, a standard deviation of 24 IQ points was found at outcome. Some children in the intensive treatment group obtained high achievement on language tests, but others remained nonverbal and severely cognitively impaired.

Given the tremendously high cost and burden of early intervention for parents and society, it is important that the efficacy of early intervention be examined more thoroughly. Moreover, additional research is needed to determine how best to transfer the university-based treatment model to community school settings, which have fewer resources available (Gresham & MacMillan, 1998). In the next sections, early intervention approaches on which data have been published are discussed.

Applied Behavior Analysis

Applied behavior analysis (ABA) refers to a set of principles, including operant learning, that are applied in an individualized, one-on-one setting to promote communication, social, adaptive, and academic functioning. ABA, specifically a traditional approach called discrete trial teaching, was first applied to children with Autism in the 1960s by \Ivar Lovaas at UCLA. Since that time, the techniques used in the ABA approach to treating children with Autism have become much more varied, with discrete trial teaching being only one of many effective ABA strategies.

In general, ABA involves the functional analysis of the child's behavior and motivation. It involves clearly defined and observable goals based on the child's abilities and challenges and regular (i.e., daily or weekly) collection of data to assess progress. These techniques are often used in home programs to supplement educational services received in the community, and a number of preschool intervention programs have modified these techniques for use in the classroom (S. R. Anderson, Campbell, & Cannon, 1994; Handleman & Harris, 1994; McClannahan & Krantz, 1994; Strain & Cordisco, 1994).

Naturalistic Interventions Incorporating Applied Behavior Analysis Principles

In recent years, more naturalistic ABA strategies have included incidental teaching (Hart & Risley, 1980; McGee, Daly, Izeman, Mann, & Risley, 1991), natural language paradigm or pivotal response training (an approach that focuses on pivotal behaviors, such as motivation and attention; R. L. Koegel & Koegel, 1995; R. L. Koegel, O'Dell, & Koegel, 1987; Laski, Charlop, & Schreibman, 1988; Schreibman & Koegel, 1996), milieu teaching (Kaiser & Hester, 1996), and the Denver model (Rogers, 1998; Rogers & Lewis, 1989). These approaches emphasize naturally occurring teaching opportunities and consequences that encourage child motivation and initiation of learning. Some approaches emphasize affective engagement and social relatedness (Rogers & Lewis, 1989).

Studies have shown that naturalistic approaches can result in more generalized responding, increased spontaneity, and improved efficiency in teaching acquisition and generalization simultaneously (Schreibman, 1997; Schreibman & Koegel, 1996). Further, these approaches have been shown to be associated with more positive affect and fewer disruptive behaviors than more traditional ABA teaching approaches (R. L. Koegel & Egel, 1979; Schreibman, Kaneko, & Koegel, 1991). These approaches are currently being used in the Walden Program at Emory University (McGee, Daly, & Jacobs, 1994), the Learning Experiences, an Alternative Program (Strain, Kohler, & Goldstein, 1996), and the Denver treatment model developed by Sally Rogers (Rogers & Lewis, 1989).

Treatment and Education of Autistic and Related Communication-Handicapped Children

The Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) program was developed in the 1960s by Eric Schopler and colleagues (Schopler, Mesibov, Shigley, & Bashford, 1984). This approach emphasizes visual structure and environmental modifications and supports to promote independence and maximize generalization of skills. The TEACCH program uses the visual, mechanical, and rote memory strengths of many children with Autism to bootstrap less developed language, imitation, cognitive, and social skills. For example, the classroom is structured to provide children with predictability and to ease transitions from one

activity to the next. Visual formats, such as picture schedules to outline tasks and show what is expected and what comes next, are emphasized, as they are easily understood and lessen anxiety, frustration, and tantrums. Such work systems are especially useful for promoting attention, independent functioning, and successful completion of tasks. Other intervention programs borrow from this approach, for example, by employing visual cues and environmental supports to increase comprehension, facilitate the exchange of information, and decrease problem behaviors (Dalrymple, 1995). In practice, many TEACCH strategies are incorporated into both traditional and naturalistic ABA programs.

Language and Communication Interventions

Improved language interventions that include motivational techniques, such as following the child's lead, emphasizing the child's motivation to respond, and providing frequent opportunities for expressive language in natural settings, have been shown to have a significant impact on the verbal communication skills of children with Autism. As many as 85% to 90% of children who began such interventions before the age of 5 learned to use verbal communication as a primary mode of communication (L. K. Koegel & Koegel, 1995; McGee et al., 1994). For children who were initially nonverbal, these interventions yielded greater increases in immediate and deferred verbal imitation, word production, and spontaneous utterances as compared to more structured approaches (e.g., discrete trial training; R. L. Koegel et al., 1987). For verbal children with delayed language, greater improvements in verbal attempts, word approximations, word production, and word combinations were found compared to discrete trial training formats (R. L. Koegel, Koegel, & Surratt, 1992). Effective procedures are currently available for teaching children with Autism to use language functions such as asking questions and other verbal initiations, which are necessary for social competence (Hung, 1977; L. K. Koegel, Camarata, Valdez-Menchaca, & Koegel, 1998; L. K. Koegel, Koegel, Shoshan, & McNerney, 1999; B. A. Taylor & Harris, 1995; Warren, Baxter, Anderson, Marshall, & Baer, 1981).

Augmentative and alternative communicative (AAC) systems are also available for nonverbal children with Autism, although problems with failure to generalize and use these systems spontaneously have been noted by some (Mirenda & Mathy-Laikko, 1989; Schlosser, Belfiore, Nigam, Blischak, & Hetzroni, 1997; Stiebel, 1999; Storey & Provost, 1996). Such systems include sign language, photographs, picture exchange systems, communication books, and computer systems, among others.

Interventions Targeting Social Behavior

A number of interventions have been shown to facilitate social interactions among children with Autism of all ages. Play-based interventions were shown to enhance the social interactions of preschool-age children with Autism with parents and other adults (G. Dawson & Galpert, 1990; Krantz & McClannahan, 1998; Rogers, Herbison, Lewis, Pantone, & Reis, 1986; Stahmer, 1995). To increase peer interactions, typically developing peer models are taught to initiate play with perseverance (Lord, 1984; Strain et al., 1996). This approach has been shown to increase the social interactions of young children with Autism, and both generalization and maintenance of effects were demonstrated (Goldstein, Kaczmarek, Pennington, & Shafer, 1992; Hoyson, Jamieson, & Strain, 1984; Odom et al., 1999; Odom & Strain, 1986; Strain, Kerr, & Ragland, 1979; Strain, Shores, & Timm, 1977). However, increases have not always generalized to untrained peers (Lord, 1984).

For school-age children and adolescents with Autism, a number of techniques have been shown to increase social interactions, including pivotal response training to teach sociodramatic role play (Thorp, Stahmer, & Schreibman, 1995), video modeling (Charlop & Milstein, 1989), direct instruction (Coe, Matson, Fee, Manikam, & Linarello, 1990), social stories (Gray & Garand, 1993), peer-mediated approaches (Lord, 1984; Lord & Magill-Evans, 1995; Shafer, Egel, & Neef, 1984; Strain et al., 1979), social skills groups (Kamps, Leonard, Vernon, Dugan, & Delquadri, 1992; Ozonoff & Miller, 1995), and visual cuing (Krantz & McClannahan, 1993, 1998).

Special Education Services

There are a number of classroom options for children with Autism, ranging from fully self-contained special education classrooms to inclusion in regular education classrooms with modifications. Federal legislation requires that schools provide fair and unbiased evaluations to determine eligibility for special services. These special services, including accommodations and objectives, form the basis of an individualized education program. However, a diagnosis of an Autism Spectrum Disorder does not always guarantee eligibility for special education services. In these cases, parents can rely on Section 504 of the Federal Rehabilitation Act of 1973, which provides for appropriate public education for all people with disabilities, with "disabilities" broadly defined. Under Section 504, educational accommodations and modifications can be stipulated to help children with Autism succeed in school. Such accommodations include posted classroom schedules, written instructions, a special

work area or divider to remove distractions, allocation of additional time to complete assignments, permission to take exams in an alternative format or to have extra time, behavior modification plans (which may involve token or other systems to reinforce appropriate behavior), handwriting alternatives (e.g., tape-recorded lectures and notes), and special help with transitions (Ozonoff et al., 2002).

Occupational Therapy, Sensory Integration Therapy, and Auditory Integration Therapy

Very few controlled studies have been conducted to examine the efficacy of occupational therapy, sensory integration therapy, and auditory integration therapy in addressing sensory and fine and gross motor impairments in Autism. Occupational therapy is a common component of intervention programs for young children with Autism and is designed to promote skill development in the context of play and adaptive behavior. Sensory integration therapy (Ayres, 1972, 1979) emphasizes the relation between sensory experiences and behavior. Strategies include the use of vestibular, proprioceptive, and somatosensory activities, such as swinging and deep pressure, to promote functional and adaptive responses to sensory stimuli. Although sensory and motor impairments are common among children with Autism, these interventions have not been well validated empirically (G. Dawson & Watling, 2000).

Adults with Autism

State government agencies that provide services to people with disabilities may provide some funding to families for vocational training and assisted or semi-independent residential living programs.

Vocational Skills Training and Employment Options

Research has shown that training in vocational and adaptive living skills is best achieved in a naturalistic setting (Schopler & Mesibov, 1983). Further, persons with Autism perform best in occupational settings that provide continued support and in vocations that involve their particular interests as well as concrete and linear processes (Mathews, 1996; Sugiyama & Takahasi, 1996). The main agency that provides vocational assistance to individuals with disabilities is the Rehabilitation Services Administration, which has chapters in each state. Employment options include sheltered employment at a job site operated by the local vocational training agency, with jobs such as mail processing, woodworking, and product assembly; secure employment, similar to sheltered employment with the exception that the adult with Autism is provided training in improving job skills and behavior, which allows for the possibility of eventually working in a more competitive and independent workplace; supported employment, working alongside adults without disabilities but with the support and supervision of a job coach (i.e., a professional or volunteer employed by the employment training agency, not the employer); and competitive employment, completely independent work requiring a mastery of both job skills and behavior (Holmes, 2000).

Residential Living Programs

In the past, the only choices of living options for adults with Autism were to keep these individuals at home with their parents or place them in a segregated institution. In more recent years, there has been a movement toward community integration, although not every area of the country offers all of the following options: independent living in a house or apartment with support services provided by agencies and families to assist with complex issues such as money management; supervised group living, usually in a residential setting with trained staff; adult foster care, wherein families receive government money to open their home to adults with disabilities; skill development homes, similar to adult foster care homes with the exception that these families are trained to work with individuals with Autism; and state-operated or privately run institutions (Autism Society of America, 2001).

Independent Living

With effective intervention and social support, many adults with Autism are able to lead independent, or semi-independent, lives that are productive and satisfying. The special strengths often associated with Autism, such as strong rote memory and excellent visualization skills, as well as artistic and musical capabilities, have allowed many persons with Autism to work productively. Social skills training and adult support groups have helped such individuals develop meaningful relationships, including friendships and marriage.

CONCLUSION

This is an exciting period in research and clinical practice aimed at helping individuals with Autism spectrum disorders, as increasingly more research is being conducted that will improve our understanding of the cause, nature, course, and treatment of these disorders. As children are recognized at earlier ages and high-quality early behavioral interventions are more readily provided, the long-term prognosis for individuals with Autism is improving, with a substantial

subgroup attaining college-level education, satisfying relationships, and independent lives.

Progress in understanding the cause, nature, and treatment of Autism will depend on an integration of scientific approaches from genetics, cognitive neuroscience, and psychology (developmental and clinical). This is a fundamental premise of the discipline of developmental psychopathology (Cicchetti, 1984, 1990, 1993). The rapidly emerging fields of the neuroscience of emotion and social behavior will inform our understanding of Autism, just as studies of Autism are informing those same fields. New findings and approaches to studying gene-environment relations and genetic regulation of brain development and plasticity surely will inform our understanding of Autism and help elucidate the effects of early intervention on brain development and behavior in Autism. Studies of the impact of early interventions on brain and behavioral functioning in young children with Autism will allow us to learn about the development and plasticity of neural systems mediating face processing, imitation, and language, among others. The genetics of Autism will allow us to understand the genetic bases of social and language abilities and help explain normal variability in the phenotypic expression of these abilities.

Discovery of Autism susceptibility genes will likely have a significant impact on how we understand the behavioral phenotype of Autism, its subtypes, early detection, and how to improve clinical intervention. For example, as genes are discovered and animal models are developed, we will begin to understand how early signs of Autism are manifest and develop and how altered experience related to brain dysfunction affects the development of later brain structures and function. We very likely will be able to identify infants at risk for Autism based on the presence of Autism susceptibility genes. This will lead to methods of very early intervention. As many symptoms associated with the Autism syndrome might be caused by the downstream consequences of an early altered trajectory of brain and behavioral development, very early intervention might potentially have a tremendous impact on outcome for many children. As such, we can hope that eventually, some cases of Autism might be preventable.

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