CHAPTER 1.2

The Behavioral Manifestations of Autism Spectrum Disorders

So Hyun Kim*, Catherine Lord†

*Autism Program, Yale Child Study Center, Yale University, School of Medicine, CT, USA  †Center for Autism and the Developing brain, in psychiatry, Weill Cornell Medical College, NY, USA

OUTLINE

Historical Perspectives on ASD Behavioral Manifestations 25
Core Features of ASD 26
Social and Communication Deficits 26
Restricted and Repetitive Behaviors and Interests 26
Heterogeneity in Behavioral Manifestations of ASD 27
Patterns of Onset and Regression 27
Developmental Trajectories 27
Intellectual Impairments 28
Language Level and Verbal IQ 28
Gender 29
Sensory and Motor Impairments 30
Adaptive Behaviors 30
Comorbidity 31
Diagnosis and Classification of ASD 32
Standardized Diagnoses 32
Classification of ASD 33
Summary and Conclusions 34

HISTORICAL PERSPECTIVES ON ASD BEHAVIORAL MANIFESTATIONS

The first documentations of autism spectrum disorders (ASD) as a syndrome were made in the early 1940s, in parallel by a psychiatrist and a pediatrician in different countries. Leo Kanner (1943) described 11 children with social aloofness, insistence on sameness, and language delays or oddities. At about the same time, Hans Asperger (1944) described 4 children whom he called ‘little professors’ who showed social awkwardness and circumscribed interests, with intact abilities in vocabulary and syntactic aspects of language. Later, Frith (1989) compared these different descriptions of ASD, which have formed the base for conceptualizations of ASD until now.

Due to the influence of psychodynamic theories in the 1960s, many believed that autism, also known as a childhood form of schizophrenia, was caused by social deprivation and/or poor parenting (Bettelheim, 1967). However, even in the 1940s, both Kanner and Asperger recognized familial, and presumably genetic, qualities that they observed in children with ASD in the parents of their child-patients. These broader phenotypes, believed to run in families, are being studied currently but it was not until the late 1960s that a number of clinical researchers began to question the psychodynamic approach, and suggested that ASD was a neurologically based disorder. In fact, researchers have found associations between autism and seizures, intellectual disability, language, and cognitive deficits arising from attentional difficulties and sensory and vestibular systems (Herme-lin and O’Connor, 1970; Rimland, 1964; Rutter and Schop-ler, 1978). In addition, Folstein and Rutter’s (1978) twin study found much greater concordance for autism in monozygotic than dizygotic twins. However, identical twins with autism-related symptoms were NOT identical in ASD symptoms, providing important evidence for
another feature of ASD – heterogeneity – which was found even within the restricted range of identical genotypes in identical twins.

Shortly thereafter, another group of researchers carried out an epidemiological study of children in London, and described a triad of impairments in social reciprocity, language comprehension, and play (Wing and Gould, 1978). This led to a broader definition of autism, and the term ‘pervasive developmental disorders’ (PDD) was used in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) and the International Classification of Diseases code (ICD-10), which determine current diagnostic categorizations (APA, 1994; WHO, 1990). In the past few years, professional and parent advocacy groups have strongly argued for its replacement by *autism spectrum disorders* (ASD), a more straightforward term. It has been suggested that the term ASD reflects *autism* as the best-characterized core syndrome, within a *spectrum* of the disorder, distinguished from autism by several factors as well as severity within those factors, thus constituting a spectrum.

**CORE FEATURES OF ASD**

**Social and Communication Deficits**

In the past 20 years, our understanding of social and communication deficits in individuals with ASD has become increasingly refined. In the DSM-IV (APA, 1994) and the ICD-10 (WHO, 1990), social and communication impairments in autism are conceptualized as separate entities. Existing criteria distinguish the communication deficits in autism, such as severe delays in expressive language level, as a separate symptom domain from social impairments. However, research on the behavioral manifestation of ASD highlights that several communication impairments in ASD, such as limited engagement in social interactions, difficulties in reciprocal conversation, and limited gestures, are both social factors and communication (Snow et al., 2009). Moreover, several recent studies have also shown that it is more valid and parsimonious to think of the social and communication symptom domains as a single factor rather than being separate (Gotham et al., 2007; Kim and Lord, 2011a).

There are several aspects of the communication impairments in ASD which go beyond speech/language delays. Language delays in individuals with ASD are not compensated by other modes of communications, such as eye contact, gestures, and facial expressions, as one would expect to see in other populations. Problems with speech quality have been noted in individuals with ASD (e.g., unusual prosody, rhythm) as well as a tendency towards using repetitive speech patterns such as stereotyped speech or delayed echolalia (e.g., repeating lines from a Disney movie).

Children with ASD show delays or failures to achieve various social communication milestones during the first year or two of life. As infants, children later diagnosed with ASD often show difficulties such as following another person’s shift in gaze, smiling at someone who smiles or vocalizes at them, and vocalizing ‘back’ to someone who is talking to them (Baranek, 1999). As they become older and more verbally fluent, children and adolescents with ASD show impairments in reciprocity while conversing with others, such as building on what the other person says or listening to how someone else feels about a particular experience. Other conversational deficits include difficulties initiating and maintaining meaningful conversation (e.g., not responding to others’ leads or questions).

Other social and communication deficits occur in different developmental milestones such as complex imaginative play, cooperative play in a group, and gestures (APA, 2000). Many individuals with ASD whose verbal abilities are intact still tend to use limited gestures that are not well integrated with other modes of communication (e.g., eye contact, vocalizations). All of these deficits and delays may negatively affect the development of meaningful social relationships with peers and others.

**Restricted and Repetitive Behaviors and Interests**

Another hallmark of ASD is restricted and repetitive behaviors and interests (RRBs). Based on the proposed DSM-5 criteria of ASD (APA, 2010), RRBs include a very broad category of behaviors such as intense preoccupations and interests (e.g., having very specific knowledge about vacuum cleaners); adherence to specific, nonfunctional routines (e.g., insisting on taking a certain route to school); repetitive motor manners (e.g., hand flapping); and preoccupation with parts of objects (e.g., peering at the wheels of toy cars while spinning them).

Many examples of RRBs represent deviance because the presence of most of these behaviors is generally considered abnormal at any age. However, during infancy and toddlerhood, some of the behaviors conceptualized as examples of RRBs have been found to be also present in typically developing children and children with other non-ASD developmental disorders (Charman and Baird, 2002; Kim and Lord, 2010; Ventola et al., 2006). For example, some children with other developmental disorders such as intellectual disabilities without autism have been found to show
some types of RRBs such as unusual sensory interests and complex mannerisms. These kinds of RRBs have been usually conceptualized as ‘lower-order’ RRBs that are associated with lower intellectual functioning (Turner, 1999). However, even though RRBs have been observed in very young children without autism, they have been found to be significantly more prevalent and/or severe in children and adolescents with ASD aged 1 to 20 years than those with other developmental disorders, or in typically developing children and adolescents (Kim and Lord, 2010; Richler et al., 2007; South et al., 2005).

Previous studies have examined heterogeneity in RRBs using factor analyses and found support for two different RRB factors: repetitive sensory-motor behaviors (RSMB; e.g., hand/finger mannerisms, unusual sensory interests, repetitive use of objects, complex mannerisms) and insistence on sameness (IS; e.g., difficulties with change in routine, compulsions/rituals, unusual attachment to objects; Bishop et al., 2006; Szatmari et al., 2006). These different types of RRB vary in their associations with NVIQ and age. For example, studies have found that RSMB, including sensory interests, hand and finger mannerisms, and complex mannerisms, were negatively associated with NVIQ and stable over time (Kim and Lord, 2010; Richler et al., 2010). While RSMB was frequently associated with lower cognitive and adaptive functioning, IS had been shown to be relatively independent of other phenotypic features (Richler et al., 2010). These different types of RRB also varied in their trajectories over time (see below). Some of these behaviors overlap with symptoms of other disorders, including obsessive-compulsive disorder (OCD; Leyfer et al., 2006).

In addition to the RSMB and IS factors, Lam and colleagues (2008) recently reported a third factor, circumscribed interests (CI), which included behaviors such as intense, focused hobbies; strong preoccupations with particular topics (e.g., Egyptian history, sewer systems); and unusually strong attachment to certain objects. In this study, CI was found to be independent of participant characteristics such as gender, age, and IQ, as well as presence of language loss/regression and autism symptoms. These results suggested that CI might be more specific to autism than RSMB and IS, as the latter two are found among other non-ASD developmental disorders. It was also argued that there have been no other psychiatric and developmental disorders that include CI as a manifestation of RRBs. In addition, Lam et al. (2008) suggested that the CI and IS factors may be of use in genetic investigation since both factors showed significant familial associations. Research has been limited in this area and the results from different studies have varied by sample and analytical methods, thus replication is needed.

**HETEROGENEITY IN BEHAVIORAL MANIFESTATIONS OF ASD**

Behavioral manifestations of ASD vary widely from one individual to another. This heterogeneity is impacted by variability in different factors, such as developmental trajectories, level of language, cognitive ability, gender, adaptive behaviors, and sensory and motor impairments. Given the extreme heterogeneity in behavioral manifestations of ASD, it is not clear whether the same etiological factors can explain different phenotypes (e.g., a nonverbal child with severe intellectual disability and verbally fluent child with advanced intellectual functioning; Lord and Corsello, 2005). These groups of children would also differ in their response to interventions. Thus, it is important to review past literature to examine how heterogeneity in behavioral manifestations of ASD is affected by variability in other factors.

**Patterns of Onset and Regression**

Some children with ASD start to show symptoms that are specific to ASD as early as 8 months (Watson et al., 2007). Patterns of onset of ASD have been examined, particularly in children who exhibit a loss of language and/or social skills in the first few years of life. Regression is highly specific to ASD. Some children who show loss in the domain of language then regain skills close to typical development prior to disruption, but others do not (Pickles et al., 2009). However, Lord et al. (2004b) also argued that, for many children with language loss, development prior to loss was rarely reported as entirely normal. In addition, a sample of multiplex families in which both affected family members had a history of regression showed an evidence of linkage on chromosome 7q and 21q, including regions containing genes expressed in fetal brain (Molloy et al., 2005). On the other hand, several studies found that children with a history of regression, by later childhood, do not show differences in autism symptom severity, intellectual functioning, adaptive behaviors, seizures, and gastrointestinal difficulties compared to children without a history of regression. Many of these studies have relied on retrospective parent-reporting of regression, which may not capture the more subtle losses observed in prospective studies (Ozonoff et al., 2011).

**Developmental Trajectories**

Past studies generally report overall gains in abilities for children with ASD over time, with considerable variability in outcomes (e.g., Mawhood et al., 2000; Sigman and Ruskin, 1999). Even though the diagnosis of autism...
has been found to be reasonably stable from the second or third year of life to early childhood and adolescence, different symptom domains or abilities show different trajectories (Lord et al., 2006; Moore and Goodson, 2003). Using a sample of 26 children with ASD, Charman et al. (2005) found that the heterogeneity in the severity of symptoms, language levels, and nonverbal IQ scores increased over time from 2 to 7 years of age. In addition, communication skills have been found to show variability in trajectory from large gains to decreases in verbal skills over time relative to age norms (e.g., Anderson et al., 2007; Charman et al., 2005; Sigman and McGovern, 2005). RRBs have also shown variability in trajectories, showing both increases and stability over time depending on different samples and age groups (Charman et al., 2005; Piven et al., 1996; Starr et al., 2003).

Many studies have reported improvements in ASD symptoms over time. For example, improvements in adaptive behavior and social responsiveness have been reported from early childhood to late adolescence (McGovern and Sigman, 2005). In this study, parents of individuals with ASD reported fewer symptoms in the areas of socialization and RRBs when their children were in adolescence than in early childhood.

Even though some improvements have been observed from early childhood into teen years, adolescents with ASD continue to experience significant degrees of autism symptoms and dependency despite a small subgroup with more favorable adult outcomes (Seltzer et al., 2004). Although autism symptoms and maladaptive behaviors in adolescents and young adults with ASD showed improvements during the secondary school years, improvement may slow after high school exit for internalizing behavior problems and most autism symptoms (Taylor and Seltzer, 2010). Thus, developmental trajectories and prognoses of ASD are quite variable, and are linked to factors such as the severity of autism specific difficulties in social and communication functioning and repetitive behaviors, and the general level of functioning, including adaptive behaviors and intellectual functioning.

**Intellectual Impairments**

Cognitive abilities observed in ASD range from severe intellectual disability to scores in the superior range on tests of intellectual functioning. In the past, it was believed that more than 50% of individuals with ASD had nonverbal IQ scores below 70 (e.g., mild to severe intellectual disability). However, recent studies have suggested that the proportion of children with ASD with nonverbal IQ scores below 70 is somewhere between 20 and 50% (Charman et al., 2011). In addition, nonverbal IQ scores in most children with ASD are found to be stable over time from age 2 to later school age.

Research has also focused on examining the differences in cognitive functioning between Asperger syndrome (AS) and those referred to as ‘high functioning autism’ (HFA). In the DSM-IV, AS is differentiated from autism by the absence of a history of language delay. Individuals with HFA generally include those who have IQs in the average to above average range. Studies examining the differences in cognitive functioning between these two groups have provided mixed results. For instance, the results of some studies have suggested that individuals with AS have higher verbal and/or nonverbal IQs than those with HFA (e.g., Klin et al., 1995). In contrast, results from other studies have indicated that there is no difference between these groups (e.g., Ozonoff et al., 2000).

Individuals with ASD have also varied in their IQ profiles, specifically in the discrepancy between verbal IQ (VIQ) and performance IQ (PIQs). Earlier, it was suggested that children with ASD had relative strengths in PIQs compared to VIQs (e.g., Lockyer and Rutter, 1970). However, more recent studies have shown that, as IQs approach the average range or higher, a few individuals, though not all, have significantly higher VIQs than PIQs (Klin et al., 1995), though the most common profile was similar PIQs and VIQs (Charman et al., 2011). Individuals with discrepant cognitive profiles (VIQs < PIQs) were shown to have increased gray matter volume (Joseph, 2011).

**Language Level and Verbal IQ**

Language abilities in ASD vary from individuals who do not develop functional speech to those who are verbally fluent. In the past, it was believed that 50% of the ASD population did not acquire any functional language (Lord et al., 2004a). Overall, it has been shown that about 30% of preschoolers with ASD have no functional use of language across different diagnostic subtypes (Chakrabarti and Fombonne, 2001).

Given the tremendous variability in language levels, the presence of distinct ASD subgroups based on language profiles has been suggested. For instance, Tager-Flusberg and colleagues (2011) highlighted three language subgroups within ASD:

1. Individuals who are verbally fluent and do not have difficulties with structural aspects of language (e.g., vocabulary, syntax, phonology);
2. Individuals who acquire varying degrees of functional language, though acquisition may be delayed, development may be slowed, and they may...
have ongoing difficulties in different areas of language;
3. Individuals who remain nonverbal (i.e., do not develop the ability to speak).

Past longitudinal studies of young children with ASD have indicated that the emergence of spoken language is one of the most important variables predicting better outcomes in later childhood and adulthood (Howlin et al., 2004; Venter et al., 1992). Children who have not developed language by age 5 are more impaired on early measures of social, communication, joint attention, and imitation skills (Thurm et al., 2007). Improvements in spoken language and communication skills have become one of the main goals in early treatments of ASD (Kasari et al., 2010). A handful of past studies examined the potential factors associated with development of verbal skills in ASD. One of the most widely studied factors related to development of language skills in ASD is joint attention, which includes ‘behaviors used to follow or direct the attention of another person to an event or object to share an interest in that event or object’ (Siller and Sigman, 2002). A child’s ability to initiate or attend to bids for joint attention (e.g., pointing, showing, and alternating gaze) is a strong predictor of verbal abilities, based on multiple studies with preschoolers, older children, adolescents, and/or adults with ASD (Dawson et al., 2004; Mundy and Neal, 2001; Sigman and McGovern, 2005).

In addition to joint attention skills, the severity of autism symptoms has been also examined as one of the predictors of verbal abilities in ASD. Poor language outcomes at age 7 were associated with impairment at age 3 in the areas of restricted and repetitive behaviors and socialization (Charman et al., 2005). Compared to children with receptive language disorder only, a verbally able autism group was more impaired on language and verbal IQ measures at age 7.5 years (Mawhood et al., 2000). Moreover, preschoolers with a diagnosis of autism, compared to those with a broader diagnosis of PDD-NOS, showed poorer language outcome 2–3 years later (Charman et al., 2003), even after accounting for initial nonverbal and language scores (Thurm et al., 2007). Finally, several studies showed a relatively high concordance rate for verbal/nonverbal status in sibling and twin pairs (e.g., Spiker et al., 2001) though results were not consistent. As of now, little is known about the biological mechanisms underlying the failure to acquire spoken language (Tager-Flusberg et al., 2011).

Gender

Gender is also one of the most important factors associated with heterogeneity in ASD. ASD is approximately 3–4 times more prevalent in boys than girls (CDC, 2007). In the past, early studies reported that females with ASD were more impaired than males in both cognitive and adaptive functioning, (Lord et al., 1982; Tsai et al., 1981). Recent studies have shown more complex relationships between gender and cognitive ability. Volkmar and colleagues (1993) suggested that autism is ‘rare’ in females with average cognitive ability. Furthermore, it has been argued that the association between gender and cognitive ability might differ by simplex (families with one affected child and one or more unaffected siblings) versus multiplex status (families with more than one child affected) based on the finding that cognitive ability was less variable across genders in multiplex samples but not in simplex samples (Spiker et al., 2001). Similarly, Banach and colleagues (2008) found no significant gender differences in NVIQ for multiplex samples, but found a gender difference in NVIQ in simplex cases of autism.

Gender differences were also examined in autism symptom severity. Some past studies have shown that females demonstrate milder impairments due to less severe RRBs and more intact imitation and play skills. For example, Lord et al. (1982) found that boys demonstrated more unusual visual interests and poorer play behavior than girls, based on 384 boys and 91 girls aged 3 to 8 years. Similarly, Hartley and Sikora (2009) found that preschool-age boys showed more RRBs compared to girls. However, a specific subtype of RRB, ‘insistence on sameness’, was found to be independent of gender in past studies based on young children, adolescents, and adults with ASD (Hus et al., 2007; Richler et al., 2010).

The findings with respect to the relationship between gender and social and communication deficits are less clear than those on RRBs. For samples of school-age children, no gender differences were found on clinical ratings of social relatedness and interest (Lord et al., 1982), while more recent work on toddlers with ASD suggested that boys demonstrated significantly better adaptive communication and less clinical impairment than girls in pragmatic and nonverbal forms of communication (Carter et al., 2007; Hartley and Sikora, 2009). On the other hand, McLennan et al. (1993) reported that male children under 5 years of age with autism showed significantly greater impairments in communication and social interaction, while after age 10, females in adolescence and adulthood demonstrated poorer current social functioning, as assessed by a distal outcome, accounted for by a lower likelihood of friendships (McLennan et al., 1993). Although the results from the previous studies are inconsistent, these studies point to the possibility of greater symptom expression in males. Future studies, however, should further examine the nature of autism.
of gender differences in social and communication functioning.

Various theoretical explanations have been suggested for the gender differences manifested in ASD. One prominent theory is that some gender differences in autism are a reflection of the sexual dimorphism in the normative population with respect to nonverbal and verbal functioning (Wing, 1981). It has been also suggested that females have less brain lateralization (and therefore require greater brain damage to be affected with autism), which may be associated with lower NVIQ scores in females than those of males (Baron-Cohen et al., 2005; Lord et al., 1982; Wisniewski, 1998). Thus, it is possible that the relationship between gender and the phenotypic expression of autism may be an interaction between changes in brain function necessary for autism impairment to occur and the greater lateralization of brain functioning in the normative male population.

Genetic studies have also provided inconsistent findings on gender differences. Specific linkage associations with male-only families and families including females have been found in some genetic studies (Lamb et al., 2005; Stone et al., 2004). Moreover, the proportion of individuals carrying de novo copy number mutations is lower (1.8:1 male:female) than the overall ratio of affected males:females in the population (Sebat et al., 2007). Even though results have not been always consistent, most evidence points to the possibility that the gender differences in autism symptom manifestations have strong neurogenetic components.

**Sensory and Motor Impairments**

Even though sensory and motor impairments are not currently part of diagnostic criteria, parents of children with ASD often report abnormal sensory behaviors and deficits in motor skills. Both increased and decreased responsiveness to sensory stimuli have been observed in children with ASD (Rogers et al., 2003). For instance, some individuals with ASD may visually inspect others by peering out of the corners of their eyes or examining things at very close range. Others may show extreme disturbances associated with certain tactile sensations such as brushing, washing, or cutting hair and strong resistance to wearing socks or shoes. Other common complaints include severe behavioral reactions to loud or unusual noises or sometimes even common sounds such as singing or coughing. One caveat is that sensory-seeking behaviors and strong disturbances are not unique to autism, but are also prevalent in children with general intellectual disabilities. However, the severity and frequency of sensory impairments have been found to differentiate children with ASD from those with other non-ASD disorders (Kim and Lord, 2010).

Motor impairments have been also reported to be prevalent in individuals with ASD. Up to 33% of cases of individuals with ASD show delays in motor milestones (Mayes and Calhoun, 2003). Some children with ASD, though not all, show problems with coordination and balance (Ghaziuddin and Butler, 1998), gait disturbances such as tiptoeing (Kielinen et al., 2004), and significant postural abnormalities (Minshew et al., 2004).

**Adaptive Behaviors**

Individuals with ASD, including more able adolescents and young adults with ASD, have significant impairments in adaptive behaviors (Howlin, 2004). Most children with early diagnoses of autism will not be completely independent as adults; many will need support in employment and residential living (Howlin, 2000). The standard scores of adaptive behaviors in individuals with ASD are seen to decline over time (Fisch et al., 2004). However, a significant minority of individuals with ASD, especially those with milder symptoms and fluent language skills by age 5, will be able to take responsibility for activities in daily living and complete higher education (Szatmari et al., 2003).

A typical profile of adaptive skills in ASD, as measured by the Vineland Adaptive Behavior Scales (Sparrow et al. 1984), is marked by greatest delays in socialization with lesser delays in communication and relative strengths in daily living skills (Bolte and Poustka, 2002). However, cognitive functioning, as one of the most important predictors of daily living skills in children with ASD, will be likely to affect this profile of adaptive behaviors in ASD. Specifically, individuals with lower intellectual functioning show more impairment in adaptive behaviors (Schatz and Hamdan-Allen, 1995). Thus, variability in adaptive functioning may be mediated by cognitive levels to a certain extent. Nevertheless, impairments in adaptive behaviors were found even in very able children with autism who showed a notable gap between IQ and adaptive skills, which widened with increasing age (Klin et al., 2007). This implies that individuals with ASD are failing to acquire skills that are expected based on their chronological and cognitive development.

Results of studies examining relations between adaptive skills and autism symptoms have been inconsistent. Some studies have found a weak relation between autism symptoms and adaptive behavior measured using the Autism Diagnostic Observation Schedule (ADOS) and the Vineland respectively (Kanne et al., 2010; Klin et al., 2007). Others have found a moderate to strong association between adaptive behaviors and
autism severity (Perry et al., 2009). It is not yet clear whether intact cognitive skills or milder autism symptoms are necessarily protective factors in adaptive behaviors in individuals with ASD.

In addition, studies found that a significant minority of individuals with ASD showed relatively optimal outcomes (e.g., average or above average IQ, intact verbal skills, and age appropriate adaptive skills), who have been referred to as ‘more able’ children with ASD (Howlin, 2000). For example, Szatmari et al. (1989) studied a group of 26 individuals with ASD of normal IQ from 11 to 27 years. Educationally, half the group had received special schooling but the other half had attended college or university, with 44% obtaining a degree. Among these individuals, 75% had fairly intact adaptive behaviors. However, these individuals still had clear social impairments such as limited eye contact, gestures, and facial expressions. About one-third of these individuals also showed problems in initiating and maintaining conversations and two-thirds had overly formal speech. Despite these social and communication difficulties, a quarter of these individuals had dated regularly or had long-term relationships. Among 26 individuals, two people were unemployed and four were in sheltered workshop schemes; three were still studying; one worked in the family business; and six were in regular, full time employment. Five individuals lived independently and, although ten were still at home, three of these were reported to be completely independent, five required some minimal supervision, one required moderate care and one needed constant supervision. These results show that there is a significant minority of individuals with ASD who show optimal outcomes, especially those whose intellectual, verbal and adaptive abilities are fairly intact.

Comorbidity

Individuals with ASD have been found to have symptoms of many other psychiatric disorders such as attention deficits, hyperactivity, anxiety, obsessive-compulsive behaviors, depression, and even psychosis. Not all individuals with ASD show symptoms of other psychiatric disorders, but a significant proportion have been diagnosed with psychiatric disorders other than ASD. Although differentiating symptoms as either a comorbid psychiatric disorder or a manifestation of autism is challenging, the phenomenon of comorbidity is of interest to researchers because it may indicate important neurochemical, neuroanatomical, or genetic overlaps between ASD and these other disorders. As mentioned above, intellectual disability (ID) is one of the most commonly diagnosed disorders in individuals with ASD, and it has been suggested that the proportion of children with ASD with nonverbal IQ scores below 70 is somewhere between 20 and 50% (Charman et al., 2011). Besides ID, the most commonly recognized co-occurring symptoms in individuals with ASD are attention deficits and hyperactivity and/or anxiety disorder (Goldstein and Schwebach, 2004; Kanne et al., 2009). By definition according to the DSM-IV, an ASD is an exclusionary criterion for making an attention-deficit/hyperactivity disorder (ADHD) diagnosis. However, about one third of individuals with ASD show attention deficits and hyperactivity symptoms which would qualify for a diagnosis of ADHD (Goldstein and Schwebach, 2004). A recent population-based study based on a sample of 112 10-14-year old children with ASD found that about 28% met the DSM criteria of ADHD and another 28% for oppositional defiant disorders (Simonoff et al., 2008). Thus, in the next edition of the DSM, it is likely that individuals with ASD will be able to receive the diagnosis of ADHD if their symptoms meet the criteria for the disorder (APA, 2010).

Past studies have also shown that more able individuals with ASD experience higher levels of internalizing symptoms such as anxiety and depression than typically developing individuals (Gillott et al., 2001; Kanne et al., 2009). Leyfer et al. (2006) found that high proportions of individuals met the criteria for different anxiety disorders among a sample of 109 children and adolescents with ASD. In their study, about 44% of the sample with ASD met the DSM criteria for specific phobia, 37% for obsessive compulsive disorder, and 12% for separation anxiety. In addition, about 10% of the sample had a history of major depressive disorder. A recent population-based study by Simonoff and colleagues (2008) also found anxiety disorders to be one of the most common comorbid diagnoses in individuals with ASD. In this study, about 29% of children from 12 to 14 years of age met the DSM criteria for social anxiety. Mazurek and Kanne (2010) also reported significantly elevated symptoms of anxiety and depression in a sample of 1,202 children between ages of 4 and 17, especially those with higher IQ scores. In addition, depression symptoms have been also prevalent in individuals with ASD, especially for those with Asperger syndrome or high functioning ASD, with comorbidity rates as high as 30% (Ghaziuddin et al., 2002; Wing, 1981).

It is not yet clear whether the behavioral and emotional problems that are found in individuals with ASD are truly comorbid or secondary to the core ASD symptoms. For example, Georgiades et al. (2010) found, using a principal component analysis (PCA) with items in the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and the Child Behavioral Checklist (CBCL; Achenbach and Rescorla, 2000) that the emotional and behavioral problems in ASD loaded
highly on components associated with autism symptoms. It is possible that symptoms such as anxiety may stem from an awareness of social and other core deficits of ASD (Bellini, 2004; Chamberlain et al., 2007). It is also known that higher IQ scores can be associated with greater anxiety (Sukhodolsky et al. 2008), which might suggest that individuals with ASD with more insight and self awareness may experience higher levels of anxiety symptoms (Mazurek and Kanne, 2010). Further research is warranted to examine the relationship between the symptoms of ASD and behavioral and emotional problems.

DIAGNOSIS AND CLASSIFICATION OF ASD

Standardized Diagnoses

A diagnosis of ASD is a diagnosis made purely on the basis of behavior because there is not yet a reliable biological marker for the disorder. Given the extraordinary heterogeneity in genetics and other neurobiological research, it seems likely that behavioral diagnoses will be an important part of understanding and treating these disorders for many years. Generally, the syndrome of autism is considered the most clearly defined of all the ASD and also one of the most reliably defined psychiatric disorders emerging in childhood (Volkmar et al., 1997). An experienced clinician, using standardized methods, can reliably diagnose autism in children aged 2, and sometimes even younger. Standardized diagnostic instruments based on criteria in the Diagnostic and Statistical Manual on Mental Disorders, 4th edition (DSM-IV; APA, 1994) and in the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; WHO, 1990) have created uniform standards for a diagnosis of ASD. However, diagnoses of autism versus PDD-NOS are relatively unstable, in contrast to overall diagnoses of ASD versus other non-ASD developmental disorders, which are consistent over time (Kleinman et al., 2008; Lord et al., 2011; Turner and Stone, 2007). For this reason, recently developed diagnostic instruments and criteria for toddlers and young preschoolers include classifications of ASD vs. non-ASD rather than autism, ASD, vs. non-ASD (Kim and Lord, 2011a; Luyster et al., 2009).

The diagnosis of ASD is made based on a comprehensive assessment of developmental history, cognitive and communicative functioning, and observation of autism symptoms using multiple diagnostic and cognitive instruments. Providing a comprehensive review of ASD diagnostic instruments is beyond the scope of this chapter. For this purpose, see Lord and Corsello (2005) or Worley and Matson (2011). Here, we will focus on two widely used instruments in clinical and research practice; the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000).

The ADI-R is a standardized, semi-structured, investigator-based interview for caregivers of individuals referred for a possible diagnosis of ASD. It is administered by a trained clinician with expertise in interviewing skills and knowledge of ASD. Information collected during the interview contributes to diagnostic algorithms, which provide classifications of ‘autism’ or ‘nonspectrum’. Recently, in research, an ASD cut-off was proposed to allow inclusion of children in the broader autism spectrum (Lainhart et al., 2006; Risi et al., 2006). Additionally, new algorithms have been developed for the classifications of children from 12 to 47 months of age with a nonverbal mental age of at least 10 months (Kim and Lord, 2011a).

The ADOS is a standardized, semi-structured, clinician observation for children and adults referred for a diagnosis of ASD. Like the ADI-R algorithms, the ADOS algorithms were developed based on DSM-IV diagnostic criteria. It includes activities that require 35–45 minutes to administer, and provides the clinician with the opportunity to observe the social, communicational, and restricted behaviors related to ASD. Five different modules, based on the level of language and age of the child, comprise the instrument. Children with mental ages under 15 months often meet ADOS cut-off criteria for ASD, regardless of clinical diagnosis. To address this issue, a toddler version of the ADOS (ADOS-T; Luyster et al., 2009), appropriate for children aged 12–30 months with no language or use of single words, was originally developed for research use and recently became available to clinicians.

In recent studies, it has been found that use of information from both the ADI-R and ADOS together better reflect clinical best-estimate diagnoses of ASD than when either single instrument was used alone. This is the case for toddlers and preschoolers, as well as older children and adolescents (Kim and Lord, 2011b; Risi et al., 2006). The ADI-R includes a developmental history and a detailed description of an individual’s functioning in a variety of social contexts, as well as caregivers’ perceptions of the level of impairment and/or frequency of different behaviors. The ADOS provides a summary of an experienced clinician’s standardized observations of an individual’s behaviors within contexts that elicit social initiations and responses as well as communication interchanges. These instruments make independent, additive contributions to more accurate diagnostic decisions for clinicians evaluating toddlers and young preschoolers with ASD. Combinations of alternative instruments such as the...
Social Communication Questionnaire (SCQ; Rutter et al., 2003), the Social Responsiveness Scale (SRS; Constantino and Gruber, 2000), and the Children’s Communication Checklist (CCC; Bishop, 2005) with or without ADI-R and/or ADOS may work equally to result in the most reliable diagnoses.

Classification of ASD

The recently proposed DSM-5 ASD criteria (APA, 2010) reflect the recent findings that social and communication impairments are highly associated with each other, as mentioned above. In the past, the criteria for an Autistic Disorder in the DSM-IV were determined based on three domains including communication, social interaction, and restricted and repetitive patterns of behavior and interests. However, the most recent proposal for the DSM-5 has defined ASD symptoms according to two domains: reciprocal social communication and a broad domain of restricted, repetitive interests and behaviors (see Table 1.2.1).

TABLE 1.2.1 Comparison of the Existing DSM-IV and Newly Proposed DSM-5 Criteria

<table>
<thead>
<tr>
<th>DSM-5</th>
<th>DSM-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom domains</strong></td>
<td>Three domains: Social deficits, Communication impairments, Restricted, repetitive patterns of behaviors and interests</td>
</tr>
<tr>
<td>Two domains: Social communication deficits, Fixated interests and repetitive behaviors</td>
<td>Differential diagnoses (ASD), includes autistic disorder, Asperger syndrome, childhood disintegrative disorder, and PDD-NOS*</td>
</tr>
<tr>
<td><strong>Differential diagnoses</strong></td>
<td>Severity levels</td>
</tr>
<tr>
<td>One category, autism spectrum disorders (ASD), includes autistic disorder, Asperger syndrome, childhood disintegrative disorder, and PDD-NOS*</td>
<td>Severity levels are not available</td>
</tr>
<tr>
<td><strong>Severity levels</strong></td>
<td>Severity levels are not available</td>
</tr>
<tr>
<td>Three levels of severity are available based on the level of support that the individual needs: Level 1: requiring very substantial support, Level 2: requiring substantial support, Level 3: requiring support</td>
<td>Three levels of symptom severity for social communication and RRB domains, determined by the individual’s need for support in this area (APA, 2010).</td>
</tr>
<tr>
<td><strong>Age and language level</strong></td>
<td>Examples for symptom domains for different age ranges and language levels will be provided</td>
</tr>
<tr>
<td>Separate examples for a range of chronological ages and language levels are not provided</td>
<td></td>
</tr>
</tbody>
</table>

In addition, instead of having differential diagnoses, a new category, autism spectrum disorders (ASD), will include autistic disorder (autism), Asperger syndrome (AS), childhood disintegrative disorder, and PDD-NOS in the DSM-5. Until now, children have been given differential diagnoses of milder forms of ASD, including AS and PDD-NOS, based on the DSM-IV criteria. AS has been characterized by impairments in social interaction and the presence of restricted, repetitive behaviors and interests. While onset of speech is not delayed in AS, atypicalities in communication, such as difficulties in reciprocal conversations and flat intonation are usually present. Based on the DSM-IV criteria, PDD-NOS is diagnosed when an individual’s difficulties are related to symptoms of autistic disorder, but are not enough to fully meet the criteria. Even though differentiation of autism spectrum disorder from typical development and other non-ASD disorders is done reliably and with validity, distinctions among ASD have been found to be inconsistent over time, variable across sites, and often associated with severity, language level or intelligence rather than features of the disorder (APA, 2010; Lord et al., 2011). For this reason, the differential diagnoses, such as AS and PDD-NOS, have been proposed to be included in a single category, ASD, in the next edition of the DSM. Additionally, research has consistently shown that a single-spectrum disorder with clinical specifiers (e.g., an associated genetic condition) is a better reflection of the state of knowledge about pathology and clinical presentation rather than having different categorical differentiations. The next edition of the DSM will also include three levels of symptom severity for social communication and RRB domains, determined by the individual’s need for support in this area (APA, 2010).

Another important proposed change in the DSM-5 ASD criteria is the consideration of age and language levels. When clinicians and researchers attempt to apply the criteria for individuals with ASD, developmental levels of the individuals, such as expressive language level and chronological age, must be taken into account before attempting to exemplify specific criteria. For instance, although failure to engage in simple social games (e.g., ‘Simon says’) may contribute to the diagnosis of autism in a 5-year old as part of a social communication deficit, a verbally fluent 11-year-old with ASD may be able to engage in simple social games with her parents and peers, but may not spontaneously engage in back and forth conversations. In contrast, in an 18-month-old, repetitive motor mannerisms such as jumping up and down in excitement are not a behavior specific to autism, but in a verbally articulate 13-year-old such behaviors would be a sign of possible ASD, to be considered along with other behaviors. Consequently, to improve the validity of ASD diagnosis,
clinicians must always consider developmental factors in ASD such as age and language levels.

**SUMMARY AND CONCLUSIONS**

ASD is one of the most reliably defined psychiatric disorders emerging in childhood (Volkmar and Rutter, 1995). Although diagnoses are reliable, there is still tremendous heterogeneity in behavioral manifestations of ASD. This heterogeneity is further affected by variability in other factors such as developmental trajectories, gender, level of language, cognitive functioning, adaptive behaviors, comorbidity, and sensory and motor impairments. Although interest in the neurobiological underpinnings of autism has been expanding, there is not yet a valid genetic or biological marker for ASD. Therefore, the diagnosis must be based on standardized assessments of both observable behavior and developmental history. However, the heterogeneity observed in ASD demands further investigation of how it may be associated with genetic or neurobiological correlates and pathways leading to ASD. Studies of very young children and siblings of children with ASD can offer opportunities to identify children at younger ages and to observe how the disorder ‘unfolds’ over the course of development (Szatmari et al., 2000).

**References**


Constantino, J., Gruber, C., 2005. Social Responsiveness Scale. Western Psychological Services, Los Angeles, CA.


1. AUTISM SPECTRUM DISORDERS
REFERENCES


1. AUTISM SPECTRUM DISORDERS
1.2. THE BEHAVIORAL MANIFESTATIONS OF AUTISM SPECTRUM DISORDERS


1. AUTISM SPECTRUM DISORDERS
Autism or autism spectrum disorders (ASD) are neurobiological disorders, defined by impairments in social interaction and social communication, and restricted interests and activities. ASD was first identified by Leo Kanner in 1943, who proposed that it was a biological condition characterized by ‘extreme aloneness from the beginning of life’ (Kanner, 1943, p. 248). While evidence in support of the biological and genetic roots of the disorder is now incontrovertible (Section 2), current data suggest that signs of the disorder are not present in the earliest months of life, but instead emerge during or after the second half of the first year (Rogers, 2009; Tager-Flusberg, 2010). Symptoms of the disorder, especially very early manifestations, seem to vary across individuals and emerge at different developmental stages, a pattern which reflects both the variability and plasticity of early development, and the heterogeneous nature of the disorder itself.

The search for the earliest manifestations of ASD is rooted in awareness of the significant theoretical and practical benefits that accrue from understanding its origins. On a theoretical level, identification of the earliest signs of ASD may advance our understanding of the nature of the disorder and the neurodevelopmental processes that underlie it. Identification of the earliest signs of disorder permits the careful study of developmental processes before those processes can be affected by an atypical developmental trajectory. Examination of early signs of ASD might also provide insights into the biological mechanisms that support typical social development. On a practical level, identification of early markers of ASD may facilitate earlier and more effective screening for the disorder, earlier identification of affected children, and earlier intervention for those children. Multiple studies have now demonstrated that intensive early intervention is associated with more positive outcomes for children with ASD, (Ben-Itzchak et al., 2008; Dawson, et al., 2009; McGovern and Sigman, 2005; Rogers and Vismara, 2008), and may be associated with extremely positive outcomes in a subset of children (Helt et al., 2008).

Often, intervention services cannot be provided until children obtain a diagnosis of an ASD. While parents may report concerns with their child’s social or...
Communicative development as early as 12–18 months (Stone, et al., 1994), several studies suggest that children may not receive an ASD diagnosis until they are 4 years of age or later (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators, 2007; Shattuck et al., 2009; Yeargin-Allsopp Monitoring Network Surveillance Year 2002 Principal Investigators, 2007). Children from socio-economically disadvantaged groups may be identified even later than children from the general population (Begeer et al., 2009; Dancel et al., 2008; Liptak et al., 2008; Mandell, et al. 2002). Systematic screening for ASD, based on early manifestations of the disorder, lowers the age at which children are referred for intervention, increases intervention rates to be more consistent with prevalence rates (Earls and Hay, 2006; Pinto-Martin et al., 2005), and reduces disparities in the age of diagnosis between racial and ethnic groups (Sices et al., 2003). Some authors (e.g., Dawson, 2008) have posited that early identification of children with ASD may permit intervention to alter atypical developmental trajectories that may prevent the development of the full autism syndrome.

This chapter will begin with a review of the literature regarding the earliest manifestations of ASD, including biological markers and early behavioral presentations. We will then consider the implications of those data for models of the disorder. We close the chapter with thoughts about the clinical applications of an emerging understanding of early risk processes.

**EARLY BIOLOGICAL MARKERS**

**Head Circumference and Other Growth Parameters**

Given its simplicity and non-invasive nature, head circumference has been used as a proxy of brain size in many studies of young children with ASD (see Chapter 3.1). Most head circumference studies have been retrospective, and have examined the early medical records of children with ASD. Head circumference at birth for infants later diagnosed with ASD is generally normal (Dawson et al., 2007; Dementieva et al., 2005; Fukumoto et al., 2008; 2011; Hazlett et al., 2005; Muratori et al., 2012; Torrey et al., 2004; Whitehouse et al., 2011) or smaller than normative samples of typically developing controls (Courchesne et al., 2003; Mraz et al., 2007; Rommelse et al., 2011). Most studies have found accelerated postnatal head growth in children later diagnosed with ASD (Courchesne, et al., 2003; Dawson, et al., 2007; Dementieva, et al., 2005; Dissanayake et al., 2006; Elder et al., 2008; Fukumoto, et al., 2008; Mraz et al., 2007; 2009; Muratori, et al., 2012; van Daalen, et al., 2007; Webb, et al., 2007), resulting in a larger head circumference sometime within the first three years of life (Courchesne et al., 2003; Davidovitch et al., 2011; Dawson et al., 2007; Fukumoto et al., 2011; Gillberg & de Souza, 2002; Mraz et al., 2007; 2009; Muratori et al., 2012; Webb et al., 2007). However, the timing of head growth acceleration is still debated. Many studies found that accelerated head circumference growth occurred within the first six months after birth (Dementieva et al., 2005; Fukumoto et al., 2008; Muratori et al., 2012; van Daalen et al., 2007), others found increased growth through the first year (Courchesne et al., 2003; Dawson et al., 2007; Elder et al., 2008; Mraz et al., 2007; Webb et al., 2007), and others still found rapid growth between the first and third years of life (Dissanayake et al., 2006; Hazlett et al., 2005). Nonetheless, increased head growth early in life appears to be an indicator for later diagnosis of ASD.

There has also been some association between early postnatal head circumference and later ASD symptoms. Infants who had a larger head circumference at 12 months, combined with deceleration of head circumference growth in the second year of life, were more likely to receive an ASD diagnosis in early childhood (Elder et al., 2008). Additionally, smaller head circumference at birth, larger head circumference between ages 1 and 2, and/or greater head circumference increase were associated with more severe autism symptoms (Mraz et al., 2007). Specifically, Courchesne et al. (2003) found that smaller head circumference at birth was associated with poorer verbal skills in early childhood, and greater increase in head circumference was associated with more repetitive behaviors.

In addition to head circumference, other growth parameters, such as height and weight, have been examined for the first three years of life in children with ASD. While not universal (Muratori et al., 2012; Webb et al., 2007), most studies have shown that children with ASD are significantly longer (Dissanayake et al., 2006; Fukumoto et al., 2008; Mraz et al., 2007; Torrey et al., 2004; van Daalen et al., 2007) and/or heavier (Dissanayake et al., 2006; Fukumoto et al., 2008; 2011; Mraz et al., 2007; 2009; Torrey et al., 2004) than their typically developing peers. Despite the abnormalities in length and weight, accelerated head circumference growth was often still present even after controlling for the other size variables (Courchesne et al., 2003; Dawson et al., 2007; Fukumoto et al., 2011). These length and weight findings, combined with the head circumference results, may suggest an early dysregulation of factors related to overall growth processes in children later diagnosed with ASD.

The rate of macrocephaly, or head circumference greater than two standard deviations above the mean, is 3% in the general population. Retrospective studies have found incidence of macrocephaly to be significantly
higher in infants and toddlers later diagnosed with ASD, with rates between 11 and 25% (Dementieva et al., 2005; Gillberg & de Souza, 2002; Lainhart et al., 1997; Muratori et al., 2012; Torrey et al., 2004; van Daalen et al., 2007; Webb et al., 2007). However, not all studies have found an elevated rate of macrocephaly in young children with ASD (Barnard-Brak et al., 2011; Davidovitch et al., 2011; Rommelse et al., 2011), and macrocephaly is not found in all children with ASD. One study found a much higher rate of macrocephaly in children with Asperger disorder (25%) compared to those with autistic disorder (10%), suggesting a possible difference in underlying etiology with different behavioral phenotypes of ASD (Gillberg & de Souza, 2002).

**Early Brain Abnormalities**

Over the past decade, researchers have begun to examine brain abnormalities in young children with ASD (see Section 3). Studies have noted increased whole brain volume (Courchesne et al., 2001; Hazlett et al., 2005; Schumann et al., 2010), and enlarged cerebral white (Courchesne et al., 2001; Hazlett et al., 2005; 2011; Schumann et al., 2010) and gray matter (Courchesne et al., 2001; Hazlett et al., 2005; Schumann et al., 2010) in infants with ASD. Within the cerebral cortex, the frontal lobes of very young children with ASD showed the greatest increase in both white and gray matter (Carper et al., 2002). Furthermore, cerebral white and gray matter displayed abnormal growth patterns across the early postnatal years (Schumann et al., 2010). The limited findings for cerebellar volume in toddlers with ASD have been mixed, perhaps speaking to the heterogeneity of the endophenotypes of ASD. The amygdala of very young children with ASD were also found to be enlarged (Schumann et al., 2009).

Several authors have begun to investigate electrical activity, using event-related potentials (ERP) in the brains of infants at high risk of autism (typically the siblings of children diagnosed with the disorder) in response to human faces. Elsabbagh et al. (2009) report that while the neural mechanisms that support face processing appear to be intact in high risk infants, these infants show a longer latency to direct gaze and their brains may have altered patterns of connectivity. McCleery and colleagues (2009) also investigated face processing in high-risk infants at 10 months. They report that these infants showed faster responses to objects, but did not differ from typically developing children in their latency of response to faces. They also report that high-risk infants showed reduced hemispheric asymmetry in ERP responses. Other investigators have reported similarly reduced hemispheric asymmetry in language processing in high-risk infants (Seery et al., 2010), suggesting that there may be diminished lateralization of brain function in high-risk infants during the first year of life. As Tager-Flusberg (2010) points out, these findings of differences in brain connectivity and organization emerge in the same period as the patterns of accelerated head growth described earlier.

Taken together, these neurological findings may suggest the presence of atypical brain development in very young children with ASD, which likely relates to their symptoms and functional difficulties. At the same time, the available data suggest that none of these biological markers are sufficiently reliable, sensitive or consistent across children to be used in the identification of young children with suspected ASD. As a result, most studies of early manifestations of ASD have relied upon assessment of behavioral symptoms.

**BEHAVIORAL MANIFESTATIONS IN RETROSPECTIVE REPORTS**

Research examining the early manifestations of ASD originally relied on retrospective studies using parent report of early symptoms, as well as early home videos of children who are later diagnosed with an ASD. These studies allow researchers to investigate participants with known diagnoses at one assessment point, reducing the length of data collection and cost of the studies. Generally, these studies identify symptoms evident as early as the first year of life within the domains of communication, socialization, and sensory reactivity, as well as motor behaviors. Additionally, retrospective studies have examined early symptoms evident among children who demonstrate symptoms of ASD following a marked loss of skills.

**Delayed Communication**

Retrospective studies have identified several aspects of communicative behavior that appear to differentiate infants with ASD from their typically developing peers. During the first year of life, parents’ recall of early symptoms indicated that infants who were later diagnosed with ASD were less likely to respond to their parents’ voices (De Giacomo & Fombonne, 1998). Additionally, the extent of expressive communication, including the frequency of simple and complex babbling, as well as delays in sound production, were found to distinguish 12-month-old infants later diagnosed with ASD from typically developing peers (Watson et al., 2007; Werner & Dawson, 2005; Wetherby & Prizant, 1998). However, delayed expressive communication is not a specific symptom of ASD and is often present among...
Lack of Social Responsiveness

During the first two years of life, aspects of social relatedness also appear to differentiate infants later diagnosed with ASD from infants diagnosed with developmental delays and from typically developing peers (Werner et al., 2005; Young et al., 2003). According to parental reports, infants who were later diagnosed with ASD tended to show less interest in peers, and were less likely to direct caregivers’ attention, share their enjoyment with caregivers, greet others appropriately, and initiate or respond to joint attention (Ozonoff et al., 2005; Werner et al., 2005). Additionally, parents reported that during the first two years of life, infants later diagnosed with ASD were less likely to imitate caregivers’ actions than typically developing peers. However, imitation did not reliably differentiate infants with ASD from infants with other developmental delays (Charman et al., 1997; Maestro et al., 2001; Watson et al., 2007).

When aspects of social engagement were examined using early home videos of infants with ASD around their first birthday, the results indicated that this group was less likely to maintain appropriate eye contact, respond appropriately to a smile, look at the faces of others, orient to their name or bring objects to show to their caregivers (Adrien et al., 1993; Clifford & Dissanayake, 2008; Werner & Dawson, 2005). In fact, the frequency of declarative pointing at 12 months distinguished children who were later diagnosed with ASD from typically developing peers (Osterling & Dawson, 1994; Werner & Dawson, 2005). However, the frequency of gesture use at 12 months does not appear to distinguish infants who are later diagnosed with ASD from infants later diagnosed with other developmental disorders (Colgan et al., 2006; Osterling et al., 2002). One study has suggested that the variety of gestures used at 12 months rather than the frequency may distinguish infants who go on to develop ASD from those later diagnosed with intellectual disability, with the ASD group exhibiting a restricted range of gestures (Colgan et al., 2006).

Symptoms of ASD within the communication domain become more evident during the second year of life (Chawarska & Volkmar, 2005). Most notably, delays in communicative abilities are usually observed by parents of children who go on to receive an ASD diagnosis around the age of 2 years (Young et al., 2003). According to parental reports, by the age of 24 months, comprehension of phrases is significantly weaker among children who are later diagnosed with ASD than among children later diagnosed with developmental delays and typically developing children (Tuszyńska et al., 2005). Furthermore, studies examining symptoms present around the child’s second birthday reveal that the vocalizations of children who are later diagnosed with ASD contain significantly less complex babble, single words, and phrases (Werner & Dawson, 2005; Wimpory et al., 2000).

Repellent Behaviors and Other Motor Abnormalities

Retrospective studies of repetitive behaviors in infants later diagnosed with ASD revealed that, during the first year of life, infants with ASD are more likely to display unusual and repetitive hand and finger mannerisms and engage in appropriate play less frequently than do typically developing infants (Dahlgren & Gillberg, 1989; Lord, 1995; Maestro et al., 2001; Osterling et al., 2002). However, the presence of repetitive behaviors during the first year of life is not useful in differentiating between infants who will receive an ASD diagnosis and those who will be diagnosed with a developmental delay (Baranek, 1999; Osterling et al., 2002; Watson et al., 2007; Werner & Dawson, 2005, Werner et al., 2005). Nevertheless, as they age, repetitive behaviors become more reliable in differentiating children with ASD. During the second
and third years of life, repetitive hand and finger mannerisms become more pronounced among children with ASD and less pronounced among children with other developmental delays and children who are developing typically (Chawarska & Volkmar, 2005; Evans et al., 1997; Moore & Goodson, 2003; Werner et al., 2005).

Other motor abnormalities identified by retrospective studies include lower levels of symmetry in the first months of life (Esposito et al., 2009), as well as low muscle tone and hypoactivity in the first year of life (Adrien et al., 1993; Maestro et al., 2005). Additionally, several studies suggest that infants and toddlers who are later diagnosed with ASD experience general delays in the development of motor skills (Landa & Garrett-Mayer, 2006; Ozonoff et al., 2008c). However, infants who are later diagnosed with ASD do not appear to be more delayed within the motor domain than similarly aged infants with developmental delays. This suggests that early motor delays may result from developmental disorders generally, rather than ASD specifically (Ozonoff et al., 2008c; Rogers et al., 2003).

Sensory Reactivity

Retrospective studies of sensory reactions in infants with ASD suggest that during the first two years of life, the presence of unusual sensory behaviors distinguishes infants later diagnosed with ASD from typically developing peers (Baranek, 1999; Baranek et al., 2006; Lord, 1995; Watson et al., 2007). Most commonly, atypical sensory behaviors observed during the first and second year of life in infants later diagnosed with ASD included unusual visual inspection of stimuli, aversion to social touch, and excessive mouthing (Baranek, 1999; Chawarska & Volkmar, 2005). Abnormalities in sensory reactivity are also commonly described among children with developmental delays (Osterling et al., 2002), suggesting that the presence of this behavior may not be a specific early marker for ASD.

Temperament and Regulatory Difficulties

When asked about the first year of their child’s life, parents of children with ASD often recalled that, as infants, their children exhibited extreme temperaments, describing behaviors indicative of emotional flatness, as well as irritability (Clifford & Dissanayake, 2007; Werner & Dawson, 2005). Additionally, parents of infants with ASD recalled more regulatory difficulties, including eating and sleeping difficulties, than did parents of typically developing infants. This difference in regulatory behaviors between the ASD group and the typically developing group was identified in infants as young as 3 months of age (Werner et al., 2005). However, a significant difference in regulatory abnormalities was not detected between infants later diagnosed with ASD and infants later diagnosed with developmental delays until the children were close to 2 years of age (Werner et al., 2005). This finding suggests that the presence of regulatory difficulties in infancy is not a specific indicator of ASD.

Regression

According to their parents, between 20 and 47 percent of children with ASD exhibit few symptoms until they experience a notable loss of social interest, words or communicative intent, imitative gestures, and at times cognitive abilities (Bernabei et al., 2006; Davidovitch et al., 2000; Lord et al., 2004; Ozonoff et al., 2005; Werner & Dawson, 2005). The prevalence of the regressive onset of ASD varies considerably across studies, and depends largely on the definition of the construct that is used by the study (Bernabei et al., 2006; Ozonoff et al., 2008a). Additionally, the nature and degree of the skill loss varies considerably across cases. For example, the most common loss is of language, and may involve a loss of some words or a loss of language altogether (Lord et al., 2004; Ozonoff et al., 2005; Werner & Dawson, 2005). Most commonly, regression begins when the child is between 15 and 24 months of age, after a period of typical or delayed development (Bernabei et al., 2006; Davidovitch et al., 2000; Lord et al., 2004; Ozonoff et al., 2005; Werner & Dawson, 2005).

Several studies of regression in ASD have explored the progress of development prior to the onset of the loss of skills. These studies suggest that in many cases some degree of developmental anomaly is evident during the first year of life, prior to the onset of the regression (Lord et al., 2004; Ozonoff et al., 2005; Richler et al., 2006; Stefanatos, 2008; Werner & Dawson, 2005). Most commonly, these anomalies consisted of social delays. Additionally, regulatory difficulties have been identified before the onset of regression in ASD, including frequent difficulty sleeping and hypersensitivity to sensory stimulation (Werner & Dawson, 2005; Werner et al., 2005).

Benefits and Limitations of Retrospective Research

Studies using parent report to examine early symptoms of ASD generally depend upon questionnaires and interviews that ask parents of children with ASD to recall their child’s development during infancy and toddlerhood. These studies provide considerable data from motivated observers who likely have access to the child in a variety of settings. However, the use of
parental reports is complicated by the parents’ inaccurate memory of events, biased recall, and limited access to an appropriate comparison group, all of which hinder a parent’s ability to report accurately on the timing and development of their child’s behavior (Lord et al., 2004; Reznick et al., 2007; Stone et al., 1994). Parental recall may be especially problematic when it is collected after an ASD diagnosis has been made, as parents may be unknowingly altering their reports to be more consistent with the diagnosis (Ozonoff et al., 2008a; Wimpory et al., 2000; Zwaigenbaum et al., 2007).

With the wide availability of moderately priced hand-held camcorders, retrospective studies began to rely on home videos of children later diagnosed with ASD in order to address some limitations of parental report studies. This approach has allowed access to rich behavioral samples of early childhood development, often in a natural environment, and minimized the bias introduced by parental recall of early symptoms. However, this line of research also has its limitations. The content of these videos varies considerably across studies, with some including involvement in typical family routines (e.g., bathing, eating, etc.), while others include special occasions such as birthday parties or holiday celebrations (Baranek, 1999; Werner & Dawson, 2005). This variability introduces possible differences between the content of videotapes in studies that compare children with ASD to controls that are inherent to the groups being studied (Baranek, 1999; Volkmar et al., 2007). Additionally, researchers had no control over the quality of the videotapes, the situations in which the tapes were recorded, the behaviors recorded or the impact aspects of the environment not captured on the video may have had on the behaviors of the child (e.g., prompting by a parent off camera; Colgan et al., 2006). Given these limitations, researchers increasingly recognized the need for prospective studies of children with autism from infancy through childhood.

**PROSPECTIVE STUDIES**

Prospective studies of any relatively rare disorder are prohibitively expensive and time consuming, and often lead researchers to look for high-risk samples where the chance of developing the disorder may be greater than in the general population. Studies have suggested that the siblings of children with ASD have a 3–8% risk of developing autism (e.g., Micali et al., 2004), making them an ideal candidate for studies of high-risk individuals.

Several studies have examined and followed the infant siblings of children diagnosed with ASD (ASD-Sibs) and siblings of typically developing children (TD-Sibs) in order to ascertain differences between the two groups very early in development. Bryson and colleagues (2008) developed the Autism Observation Scale for Infants (AOSI) to identify early signs of ASD in high-risk infants. Using this measure, their team found that there were no significant behavioral differences at 6 months of age (Zwaigenbaum et al., 2005). However, at 12 months, the presence of multiple risk factors on the AOSI predicted ASD classification at 2 years of age (Zwaigenbaum et al., 2005). Specific risk factors from the AOSI included atypical eye contact, visual tracking, disengagement of visual attention, response to name, imitation, social smiling, interest in social interaction, and sensory abnormalities (Zwaigenbaum et al., 2005).

In terms of developmental level, at 4 months, ASD-Sibs had lower mental scores on the Bayley Scales of Infant Development compared to siblings of typically developing children (TD-Sibs) (Gamlie1 et al., 2007). However, other studies at 6 months utilizing the Mullen Scales of Early Learning found no differences between TD-Sibs and ASD-Sibs on any domain, including Fine Motor, Visual Reception, Expressive Language, and Receptive Language (Landa & Garrett-Mayer, 2006; Ozonoff et al., 2010). By 14 months, differences were more pronounced, with consistent impairments on the Bayley Scales of Infant Development and the Mullen Scales of Early Learning for ASD-Sibs (Gamlie1 et al., 2007; Landa & Garrett-Mayer, 2006; Ozonoff et al., 2010). Language abilities were deficient on the scales of the Mullen Scales of Early Learning and other language measures by the end of the first year (Gamlie1 et al., 2007; Landa & Garrett-Mayer, 2006; Ozonoff et al., 2010; Yirmiya et al., 2006; Zwaigenbaum et al., 2005).

ASD-Sibs and TD-Sibs had similar rates of directed vocalizations at 6 months; however, by 12 months, the rate of directed vocalization by ASD-Sibs was less than that of TD-Sibs (Ozonoff et al., 2010).

Social behaviors have been extensively examined in infant ASD-Sibs. ASD-Sibs as young as 4 months showed less synchrony in self-directed social interactions with their parents than TD-Sibs (Yirmiya et al., 2006) but these differences are subtle and difficult to detect. At 6 months, there was no difference between ASD-Sibs and TD-Sibs in response to name, gaze to faces, or social smiles (Nadig et al., 2007; Ozonoff et al., 2010). By 12 months, ASD-Sibs were less likely to respond to their name and displayed fewer gazes to faces (Nadig et al., 2007; Ozonoff et al., 2010). At this age, ASD-Sibs initiated fewer low-level (making eye contact to request or reaching for the toy) (Cassel et al., 2007; Rozga et al., 2011; Yirmiya et al., 2006) and high-level (pointing or giving the toy to the examiner) behavioral requests (Cassel et al., 2007). At one year of age, ASD-Sibs also were less likely to initiate...
or respond to acts of joint attention than TD-Sibs (Rozga et al., 2011).

The still-face paradigm (Tronick et al., 1978) has been used to assess social relatedness and emotional reactivity in ASD-Sibs. During this task, after an initial baseline play period, there is a period in which the parent is socially unrelated ('still face'), followed by a reunion play period. Studies using observation of gaze as well as more sophisticated eye tracking methodologies have found that during the still-face paradigm, 6-month-old ASD-Sibs looked at their parent's face at least as often as TD-Sibs (Ibanez et al., 2008; Merin et al., 2007; Rozga et al., 2011; Yirmiya et al., 2006), although more subtle gaze differences have been identified. Ibanez et al. (2008) noted that infant ASD-Sibs less frequently shifted their gaze to and from their parent’s face and gazed away from their parent’s face for longer durations at a time. Furthermore, while Merin et al. (2007) found no group differences for gaze to face versus non-face or for specific face regions, they identified a subgroup of infant ASD-Sibs who displayed reduced gaze to their parent's eye and increased gaze to their parent's mouth.

Emotional reactivity indicators from the still-face paradigm showed that infant ASD-Sibs sometimes smiled less (Cassel et al., 2007), were upset less (Yirmiya et al., 2006), and displayed more neutral affect (Yirmiya et al., 2006) than their peers.

Temperament differences have also been found in infant ASD-Sibs. At 6 months of age, ASD-Sibs who were classified as having an ASD at 24 months had a lower activity level than TD-Sibs at 6 months (Zwaigenbaum et al., 2005). Later, at 12 months of age, compared to TD-Sibs, ASD-Sibs who received an ASD diagnosis at 24 months had more severe reactions to distress and tended to fixate on objects for longer periods of time (Zwaigenbaum et al., 2005).

Studies have also tracked visual attention and eye gaze in infant ASD-Sibs. ASD-Sibs spent less time looking at their caregivers and more time looking at non-social objects at 6 months old compared to TD-Sibs (Bhat et al., 2010). At 6 months of age, ASD-Sibs displayed no deficits on a visual orienting task (Zwaigenbaum et al., 2005). However, by 12 months, as a group, the infant ASD-Sibs performed worse on this task than TD-Sibs. Furthermore, all of the infants who showed increased disengagement received an ASD diagnosis at age 2 (Zwaigenbaum et al., 2005). Another study of 10-month-old infants showed that ASD-Sibs had prolonged latencies to disengage their attention and reduced facilitation by an attentional priming cue (Elsabbagh et al., 2009).

Taken together, these infant sibling studies suggest that there are few very early behavioral markers implicated in later diagnosis of ASD. Atypical attention and gaze seems to be one of the earliest indicators, and subtle differences in these behaviors may be evident, at least in a subgroup of children with ASD, as early as 6 months. However, as other investigators have noted, the majority of infants at risk who will later be diagnosed with ASD, have no discernible signs at 6 months (Rogers, 2009; Tager-Flusberg, 2010). By 12 to 14 months, numerous behavioral markers emerge, including atypical social development, delayed communication development, and temperamental differences.

Studies of 12- to 24-Month-Olds with ASD

Given clinicians’ increasing ability to diagnose autism in toddlers (Chawarska et al., 2007), there is increasing data available about the earliest signs of the disorder in children who meet criteria for the diagnosis. Participants in these studies comprise a broader range of children than those in studies of high-risk siblings, since they include children who may not have any increased genetic vulnerability to the disorder. To the extent that these studies include children identified after 1994, when diagnostic standards were expanded, they include an even more heterogeneous group. The following review includes prospective studies of high-risk siblings, prospective studies from the general population, and cross-sectional designs.

During the second year of life, children with ASD display deficits in the frequency of vocalization directed to others and demonstrate a significantly lower rate of communication than typical peers (Chawarska et al., 2007; Shumway & Wetherby, 2009; Wetherby et al., 2007). When infants with ASD did vocalize, their prosody was often atypical (Wetherby et al., 2004). At 12 months, children with ASD understood fewer words and phrases than controls; these deficits persisted at 18 months, when children with ASD also produced fewer words (Mitchell et al., 2006). Between ages 1 and 2, children with ASD were impaired in their use of pointing and other communicative gestures (Chawarska et al., 2007; Shumway & Wetherby, 2009; Wetherby et al., 2007). Imitation of gestures and actions was also poorer in young toddlers with ASD compared to controls (Charman et al., 1997; 1998; Young et al., 2011).

Within the social domain, between 12 and 24 months, children later diagnosed with ASD were less likely than their typical peers to orient to their name (Brian et al., 2008; Chawarska et al., 2007; Wetherby et al., 2004), make appropriate eye contact (Brian et al., 2008; Chawarska et al., 2007; Wetherby et al., 2004), engage in reciprocal social smiling (Brian et al., 2008; Chawarska et al., 2007), or show social interest and affect (Brian et al., 2008; Chawarska et al., 2007; Wetherby et al., 2004). Toddlers with ASD were also less likely to direct
facial expressions to others (Chawarska et al., 2007; Wetherby et al., 2004), integrate gaze with vocalizations (Chawarska et al., 2007; Wetherby et al., 2004), or request, give, or show (Chawarska et al., 2007; Wetherby et al., 2004). Very young children with ASD often had impaired initiation of joint attention (Chawarska et al., 2007) and, less frequently, impaired response to joint attention (Charman et al., 1997; 1998; Chawarska et al., 2007; Shumway & Wetherby, 2009; Sullivan et al., 2007; Wetherby et al., 2007) in the second year of life. Toddlers aged 12–24 months with ASD paid less attention to and expressed limited concern for another person’s distress compared to typically developing peers (Charman et al., 1997; 1998; Hutman et al., 2010). Between 1 and 2 years of age, infants with ASD spent less time looking at people, more time looking at objects, and less frequently shifted their attention between social and nonsocial stimuli (Swettenham et al., 1998). In one of several studies to use eye-tracking methods in young children, Jones, Carr, and Klin (2008) reported that 2-year-old children with autism spent less time looking at the eyes of approaching adults, and more time looking at their mouths than either typically developing children or children with non-autistic developmental delays. In addition, children in their sample who spent less time looking at adults’ eyes exhibited greater levels of social disability. In a second study, Klin et al. (2009) found that 2-year-olds with autism attend more readily to physical contingencies than to biological motion. Jones and Klin (2009) suggest that failure to attend to the eyes and to human motion may suggest that children with autism learn in a manner dominated by physical rather than social information, and that pattern may have important consequences for social development. These authors also suggest that tracking eye gaze in young children may provide an early biomarker for ASD.

During the second year of life, children with ASD demonstrated greater frequency and duration of repetitive and stereotyped behaviors with objects (Morgan et al., 2008; Watt et al., 2008; Wetherby et al., 2004) and body (Watt et al., 2008), as well as more sensory behaviors (Watt et al., 2008) compared with typically developing and developmentally delayed controls. Twelve-month-olds with ASD were more likely than developmentally delayed children (Rogers et al., 2003; Stone et al., 1997), although imitation skills improved in children with ASD between ages 2 and 3 (Stone et al., 1997). Deficits in imitation were not associated with fine motor, gross motor, or praxis difficulties (Rogers et al., 2003). Imitation skills were correlated with autism severity and joint attention skills for toddlers with ASD (Rogers et al., 2003).

Socialization skills remain consistently impaired in children with ASD between 24 and 36 months, except for improvement in response to joint attention (Chawarska et al., 2007; Goldberg et al., 2005). However, initiation of joint attention remains impaired (Chawarska et al., 2007; Goldberg et al., 2005). Furthermore, in the third year of life, young children with ASD continued to make less frequent eye contact and engage in less turn-taking behaviors than their typical peers (Goldberg et al., 2005).

Differences in affect and behavioral regulation have been noted between young children with ASD and
typical peers. At age 2, children later diagnosed with ASD had less positive affect, more negative affect, and greater difficulty controlling attention and behavior than typically developing children (Garon et al., 2009). Children later diagnosed with ASD also were less likely to find social cues rewarding (Garon et al., 2009). During the third year of life, compared with typically developing children and children with developmental delays, children with ASD were more likely to use objects repetitively, engage in complex mannerisms with their bodies or hand and finger mannerisms, have difficulty with changes in routine, or have unusual attachments to objects (Richler et al., 2007). Additionally, compared with typically developing children, children with ASD had more unusual sensory interests, unusual preoccupations, and abnormal or idiosyncratic responses to sensory stimuli (Richler et al., 2007).

Another study found that higher-level repetitive behaviors, such as verbal rituals, unusual preoccupations, compulsions, and difficulty with change, were more common in children diagnosed with ASD than children who are developmentally delayed without ASD, even after controlling for severity of delay, age, and adaptive functioning (Mooney et al., 2006). Conversely, lower-level repetitive behaviors, such as repetitive use of objects, hand and finger mannerisms, complex mannerisms, and self-injury, were equally common in ASD and other developmental delays, and were found more often in the third rather than fourth year of life (Mooney et al., 2006). Additionally, functional and imaginative play improved in children with ASD between 2 and 3 years of age, but still remained atypical (Chawarska et al., 2007).

Symptoms of ASD in the third year of life remain fairly consistent, although atypical communicative behaviors and stereotyped interests begin to emerge at this time.

Taken together, these data provide support for the hypothesis that the earliest manifestations of ASD are evident in the domains of attention and social motivation in the latter half of the first year of life but not before. Infants at greater risk for ASD experience a decrease in the frequency of social behaviors, perhaps especially self-initiated social overtures (Bhat et al., 2010), and in ability to shift attention flexibly, beginning between 6 and 12 months. By 12 months, infants at greater risk for ASD exhibit decreased verbal and nonverbal communicative overtures (Lander and Garrett-Mayer, 2006; Yoder et al., 2009), diminished responsiveness to name (Nadig et al., 2007), atypical object exploration, and increased repetitive behaviors (Ozonoff et al., 2008a). These behaviors may be the earliest manifestations of an atypical developmental trajectory that becomes increasingly apparent as social and communication expectations increase through the preschool years.

While studies of high-risk infant siblings have been enormously helpful in describing the early behavioral patterns that predate and may predict the development of ASD, such studies have their own limitations. First, there is considerable variability in data from sibling studies based on the age at which children are enrolled, the age to which they are followed and other variables, and these differences may affect data in unspecified ways. For example, studies which enroll children at age 12 months or later may enroll more parents who already have concerns about their child’s development (Rogers, 2009).

Similarly, the experience of growing up in a home with a sibling with autism, and the stresses that may impose on families may also affect development. Finally, it may be the case that children with a greater genetic loading for the disorder differ from children without such a loading. For example, while there is increasing evidence that high-risk sibs who later develop ASD may present repetitive behaviors in the second year of life, there is evidence that in population samples of toddlers diagnosed with ASD, repetitive behaviors may not appear until the third or fourth year. These divergent findings likely reflect the increased heterogeneity in population samples and suggest caution in the generalization of results from studies of children with high genetic loading for ASD. There are also methodological issues that render the interpretation of data inconclusive at times. The use of more experimental tools such as eye tracking and evoked potential in the next generation of studies of high-risk infants may help clarify some of the inconsistent findings in the existing literature.

THEORETICAL CONSIDERATIONS

What do the data regarding the earliest manifestations of ASD suggest about the nature of the disorder? At present, opinions vary. Review of the available literature suggests that very early social and communicative deficits define ASD and that the deficits in social functioning appear prior to deficits in communicative skills (Fein et al., 2011). Some researchers argue that evidence of early deficits in social responsiveness (e.g., deficits in joint attention, response to name) support the view that autism disrupts motivation for social engagement, and the absence of such motivation derailed typical developmental trajectories and results in the multiple impairments seen in older children with autism (Dawson, 2008; Fein et al., 2011). As early as 6 months, diminished social motivation may direct children’s attention away from human faces and toward inanimate objects. That disengagement may imperil developing abilities to read social communication and to share experience. It may also undermine the ability to shift attention flexibly,
both of which would have negative effects on cognitive development downstream. The establishment of atypical developmental trajectories may reduce opportunities for experience-dependent brain development, leading both to behavioral patterns characteristic of the disorder and to atypical brain development. Dawson (2008) argues that this may be best understood as a set of genetically mediated risk processes that leave children unable to access and benefit from exposure to environmental interactions. Early identification of such risk processes might permit the interruption of those negative cascades at both the neurological and the behavioral level, and permit the development of compensatory processes or the restoration of more typical trajectories. Such a model, while speculative, has the potential to account for much of the variability in the presentation of ASD, and for the variable effect of intensive intervention on developmental processes. While intervention is almost uniformly helpful, it is clearly of greater help to some children than to others (see Helt et al., 2008 for review), and much of the variability in outcome appears to be related to characteristics of the child. Greater understanding of those characteristics would permit the more careful specification of interventions tailored to the needs of individual children.

Other researchers take the opposite view, and argue that the rapid deceleration in developmental progress seen in children at risk of autism between the ages of 6 and 12 months includes a variety of skills not related to social function, and sometimes regarded as secondary to the diagnosis. Rogers (2009) and Tager-Flusberg (2010) argue that emerging evidence suggests that high-risk children who later receive a diagnosis of an ASD present a variety of atypical behaviors beginning at approximately 12 months. These include increased irritability, sensory reactivity, increased activity, and possibly motor delays, although the data in support of each of these changes is much less robust than the data cited earlier in support of changes in social responsiveness. Rogers interprets the onset of broader symptoms as suggesting that autism disrupts multiple aspects of development simultaneously, and can no longer be regarded as a primarily a social communicative disorder (Rogers, 2009). Rather she regards it as a disorder that affects multiple domains of function and alters the course of development across multiple areas.

Similarly, Tager-Flusberg (2010) suggests that ASD is a complex syndrome that develops gradually and reflects alterations in expected developmental pathways in multiple domains. There is no single domain of function or behavioral manifestation that predicts the development of ASD symptoms or the prognosis for an affected child. In some developmental domains, the onset of ASD is characterized by slowed development or a plateau of progress; in other domains, including social functioning, there may be a loss of previously acquired skills. Tager-Flusberg posits that the widely held belief that regression characterizes the presentation of a subset of children with ASD may be in error; rather she argues that regression, specifically in the area of social communication skills may be characteristic of all children with ASD and may be a consequence of a broader developmental anomaly. Both Rogers and Tager-Flusberg suggest that data from studies of high-risk siblings have suggested a significant refinement in our understanding of the nature of ASD, and especially in the role accorded to social-communicative functioning, but they acknowledge that there is much we do not yet know. Among the remaining questions they note the following: What neural mechanisms underlie the atypical developmental trajectory exhibited by young children with ASD? What precipitates the divergence of their developmental trajectory from the more typical course? Is ASD driven by a loss of interest in the social world or an exaggerated interest in the world of objects, or an inability to shift attention flexibly? These and many other questions await more careful examination of early signs of the disorder, including more data from experimental paradigms such as eye tracking and ERP.

CLINICAL IMPLICATIONS

Understanding of the early manifestations of ASD has already resulted in an improved ability to screen children for early signs of the disorder, with the resulting recommendation that all children be screened as part of routine pediatric care at age 18 and 24 months (Council on Children with Disabilities, 2006). Several groups of researchers have developed successful screening tools for toddlers based on early signs of social-communicative impairment (e.g., The Modified Checklist for Autism in Toddlers (M-CHAT) (Robins et al., 2001), or the Infant–Toddler Checklist (ITC) (Wetherby et al., 2008). These measures have been recently reviewed (Barton et al., 2011) and will not be considered in detail here. Both the M-CHAT (Chlebowski, 2011; Kleinman et al., 2008; Robins et al., 2001) and the ITC (Wetherby, 2010; Wetherby et al., 2008) consistently identify children at risk of ASD, and both require the use of follow-up measures to reduce their false positive rate. Other researchers have attempted to extend early screening to children younger than 16 months. Dietz et al. (2006) screened 31,724 14–15-month-olds and reported limited sensitivity in this age group. Pierce et al. (2011) used the ITC to screen 10,479 infants aged 12 months. Both groups of investigators report a significant false positive rate as well as difficulty differentiating children with ASD
from those with other developmental concerns. Both Dietz et al. (2006) and Pierce et al. (2011) also note that many parents refused follow-up evaluations due to their low index of concern. Rogers (2009) notes that the enormous variability in the earliest signs of ASD has important implications for screening. She argues that autism screenings will have to be administered repeatedly, perhaps through age 36 months in order to identify all affected toddlers, and they should be designed to identify toddlers with less severe signs as well as those with clear-cut symptoms of ASD.

Awareness of early signs of ASD has also influenced the prevailing standards for the diagnostic evaluation of young children. The development of the Autism Diagnostic Observation Schedule (Lord et al., 2000) provided a reliable and valid tool for the assessment of reciprocal social interaction and social communication; refinements to the scoring algorithm now include increased attention to restricted interests and repetitive behaviors (Gotham et al., 2007). While diagnosis of children younger than 2 is increasingly common, the variability in early presentation of ASD symptoms as well as the rapidity of developmental change in young children warrants special diagnostic considerations. Many of the behaviors that mark early social development must be assessed relative to a child’s developmental age. Children of any age whose developmental functioning is typical of children aged 10–12 months or younger cannot be expected to exhibit the social behaviors (e.g., pointing, gaze shifting) which characterize normative development, and the absence of those behaviors cannot always be interpreted as indicative of disorder. Nor are there reliable behavioral markers which might indicate an atypical trajectory in those children.

Recently proposed practice parameters recommend that the diagnostic process include standardized assessment of communication, and cognitive and adaptive skills as well as the structured observation of social, communicative, and play skills, and repetitive interests and behaviors. Data must be obtained both from detailed interviews with caregivers, and from systematic and structured observation of the child in settings designed to encourage social engagement. Finally data must be interpreted in a developmental framework by clinicians with expertise with infants and toddlers with ASD (Zwaigenbaum et al., 2009).

Most recently, data regarding the earliest manifestations of ASD have influenced changes to the standards used to define the disorder. In the proposed revision to DSM-IV, the multiple diagnoses now subsumed under the category of Pervasive Developmental Disorders will be eliminated, in large measure because it has proven difficult to make reliable distinctions between them. Instead they will now be viewed as a continuum without specific subcategories. The disorder will be defined by two sets of symptoms. The first reflects the overlap between symptoms of social engagement and intentional communication, and focuses on deficits in both social communication and interaction. This change appears related to the increased recognition of the complex relationship between early social engagement and the development of communication strategies, and the recognition that impairments in social motivation derail development in multiple areas. The second factor includes restricted and repetitive patterns of behavior and requires at least two of four specific behaviors (http://www.dsm5.org).

While this change may reflect data from studies of high-risk siblings which supports the presence of repetitive behaviors in young children, there is concern that the requirement that such behaviors be observed in all children in order to qualify for a diagnosis on the autism spectrum may result in the exclusion of children with milder forms of the disorder, or the delayed identification of children whose symptoms, especially in the area of repetitive behaviors, develop later in childhood. Those issues are currently under discussion and await further empirical data. These and other critical questions regarding diagnosis, the potential identification of subtypes of ASD, and the development of effective treatments have clearly been informed by the research efforts reviewed here and await further study of the youngest children affected by ASD.

References


1. AUTISM SPECTRUM DISORDERS


1. AUTISM SPECTRUM DISORDERS

autism at age 2 and development of an early diagnostic service. Autism 7, 47–63.
REFERENCES


Asperger Syndrome and its Relationships to Autism

James C. McPartland*, Fred R. Volkmar†

*Yale Child Study Center, New Haven, CT, USA †Yale University School of Medicine, Yale New Haven Hospital, New Haven, CT USA

DIAGNOSTIC CONCEPT

History

In 1944, a medical student in Vienna, working on his medical school thesis, described four boys with marked social problems and poor motor skills, but highly developed verbal language, and unusual, highly idiosyncratic and circumscribed special interests (Asperger, 1944). This student, Hans Asperger, also observed that the condition seemed familial, and he used the word ‘autism’ in his original description of the condition as ‘Autistic Psychopathy’. Asperger made the important point that the special interests exhibited by these boys were maladaptive both because they interfered with learning in other areas and because they could come to dominate the family’s life. Because of the international academic impasse caused by World War II, he was not familiar with Leo Kanner’s report, published the preceding year (1943), describing the condition of early infantile autism. At that time, the current emphasis on phenomenological, research-based definitions had not yet evolved (Spitzer et al. 1978), and Asperger continued to publish on the topic until the time of his death (Asperger, 1979). Because he published in German journals, his work received relatively little attention in the English language literature at the time.

Very few English language publications on Asperger syndrome (AS) appeared for several decades after Asperger’s work. Initial publications included discussion of AS as a type of personality trait/disorder (i.e., rather than a developmental disorder; Van Krevelen, 1971), as well as redescription of some Asperger’s cases (Robinson...
Asperger syndrome (AS; Wing, 1981) has been the subject of much debate and controversy regarding its classification and diagnostic criteria. The relationship between AS and autism spectrum disorders (ASD) has been a key point of discussion, with some researchers viewing AS as a variant of autism (e.g., Wing, 1981) and others as a separate, albeit related, entity (e.g., Rutter, 1967). The diagnostic criteria for AS have evolved over time, with the DSM-IV-TR (APA, 2000) providing a distinct diagnostic category for AS, separate from autism.

Diagnostic Criteria

Current definitions maintain some continuity with Asperger’s original description of the disorder but also differ in several ways (Woodbury-Smith et al., 2005). Current diagnostic criteria in the DSM-IV-TR distinguish AS from autism primarily by adding exclusionary criteria (APA, 2000). Children with social deficits and restricted interests who do not meet criteria for autism, did not evidence frank language delay, and possess preserved cognitive ability and daily living skills qualify for AS. Specific diagnostic criteria include two areas of impairment from among the following social behaviors:

1. Inability to use multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction;
2. Failure to develop peer relationships appropriate to developmental level;
3. Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people);
4. Lack of social or emotional reciprocity.

These social impairments must co-occur with at least one area of impairment in terms of the following categories of restricted, repetitive, and stereotyped patterns of behavior, interests, and activities:

1. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus;
2. Apparent inflexible adherence to specific, nonfunctional routines or rituals;
3. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements);
4. Persistent preoccupation with parts of objects.

Additional diagnostic criteria specify that these symptoms cause clinically significant impairment in social, occupational, or other areas of functioning without a clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years) or in the development of...
cognitive ability or age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood. Finally, to be eligible for diagnosis of AS, a child must not meet criteria for another specific pervasive developmental disorder or schizophrenia. The text in both DSM-IV-TR and ICD-10 (shown in Box 1.4.1) notes that motor awkwardness and/or clumsiness are common and that, in contrast to autism, the restricted interests observed often take the form of unusual, intense, and highly circumscribed interest or interests.

Clinical Features

In many respects, Asperger’s original (1944) description continues to provide one of the best overviews of the clinical features in AS. The cases he described had major problems in social interaction. This was, and remains, the major similarity to autism. However, other features were also present, such as highly intense, idiosyncratic special interests, trouble in self-awareness, impairments with motor skills, and difficulty with social communication. These special interests became a major focus of the child’s life and often interfered with familial function. Asperger emphasized the intrusiveness of these interests on other facets of the child’s life, such as learning. The first cases were noted to have major difficulties in self-awareness – especially affective self-awareness. They tended to approach highly emotionally laden tasks in an intellectual way and this further compounded their social isolation.

Asperger also noted persistent gross and fine motor vulnerabilities. Developmentally, he noted that the cases tended to talk before they walked and that parents were often unconcerned until the child entered preschool or other settings where major problems with peers quickly surfaced. The combination of motor and social problems also made for difficulties in sports. The social presentation of these children, that is, as little professors, served to further isolate them from peers, despite some degree of social interest on their part. Although the cases had excellent basic language skills (e.g., vocabulary), they also had significant problems with nonverbal and social (pragmatic) communication skills. Voice modulation was noted to be odd, as were facial expressions and gestures. Difficulties with rigidity and social isolation also could result in behavioral difficulties, as cases balked at minor changes in routine. Finally, Asperger’s original paper also emphasized the existence of similar personality problems in family members – particularly fathers.

AS is often detected later in childhood than other autism spectrum disorders (ASD) because children with AS develop language and self-help skills on time. Furthermore, some of the prototypic characteristics of AS, such as impairments in social reciprocity and special interests, do not surface as atypical until a child reaches a developmental level when these characteristics of interaction are expected. The diagnosis of AS is most commonly made after 4 years of age (Szatmari et al., 2003) and often as late as 11 years (Gillberg & Cederlund, 2005; Howlin & Asgharian, 1999). It has

---

**BOX 1.4.1**

**ICD-10 RESEARCH DIAGNOSTIC GUIDELINES FOR ASPERGER SYNDROME**

1. There is no clinically significant general delay in spoken or receptive language or cognitive development. Diagnosis requires that single words should have developed by 2 years of age or earlier and that communicative phrases be used by 3 years of age or earlier. Self-help skills, adaptive behavior, and curiosity about the environment during the first 3 years should be at a level consistent with normal intellectual development. However, motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary diagnostic feature). Isolated special skills, often related to abnormal preoccupations, are common but are not required for the diagnosis.

2. There are qualitative abnormalities in reciprocal social interaction (criteria for autism).

3. The individual exhibits an unusual intense, circumscribed interest or restricted, repetitive, and stereotyped patterns of behavior interests and activities (criteria for autism; however, it would be less usual for these to include either motor mannerisms or preoccupations with part-objects or nonfunctional elements of play materials).

4. The disorder is not attributable to other varieties of pervasive developmental disorder; simple schizophrenia schizotypal disorder, obsessive-compulsive disorder, anakastic personality disorder; reactive and disinhibited attachment disorders of childhood.


---

1. AUTISM SPECTRUM DISORDERS
been suggested that the diagnosis of AS cannot be rendered with adequate reliability prior to age 4 (McConachie et al., 2005), though single-case studies have detected AS in children as young as 26 months (Baron-Cohen et al., 2006). Despite this pattern of later diagnosis, parents of children with AS retrospectively report concerns well before 3 years (Gilchrist et al., 2001) and, in some cases, as early as 20 months (Chakrabarti & Fombonne, 2005). Indicators in early childhood include a preference to interact with others for instrumental reasons (e.g., requesting, seeking help) rather than social reasons. Intense interests in specific topics may emerge by preschool, with social overtures consisting of attempts to draw others into this interest. Social difficulties noted outside of the familial context include failing to seek out or avoiding interactions with other children. Behavioral rigidity, in the form of ritualized daily activities or stringently adhering to a schedule, may also be evident early in life and can interfere with social interactions.

Differential Diagnosis

Given the commonality with autism in terms of severity and persistence of social deficits, the major issue regarding differential diagnosis has been differentiation from autism. In contrast to autism, language is relatively preserved, as are verbally mediated cognitive skills. Fine motor vulnerabilities can be dramatic in younger children relative to autism. For example, in contrast to a child with autism with good drawing abilities but limited vocabulary, the child with AS may produce a rather poor and immature drawing but elaborate verbiage to describe it.

Other issues arise from similarities between AS and multiple disorders described in psychiatry and other disciplines, including semantic-pragmatic disorder, schizoid disorder, right hemisphere learning disabilities, and nonverbal learning disability (Klin et al., 2005a). The concept of nonverbal learning disability (Rourke & Tsatsanis, 2000), in particular, has been of interest, since it is a syndrome associated with a number of different conditions in addition to AS. This concept focuses on a constellation of symptoms and a specific neuropsychological profile in which, in contrast to more classical autism, nonverbal skills are more impacted than verbal ones; changes in the syndrome manifest themselves over development as individuals are taught, or learn on their own, to use coping strategies bringing the verbal strengths into use in addressing areas of deficit. The DSM-IV and ICD-10 approach has drawn criticism (Leekam et al., 2000; Mayes et al., 2001; Miller & Ozonoff, 1997; Szatmari et al., 1995). For these reasons, multiple authors have proposed variant diagnostic criteria to improve upon perceived shortcomings in the current diagnostic operationalization (see Box 1.4.2).

EPIDEMIOLOGY AND COMORBIDITY

Epidemiology

ASD occur more frequently in boys than girls, at approximately a 3–4:1 ratio (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators, 2007; Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators, 2009; Fombonne, 2005). AS tends to have an even more pronounced gender bias of 9 to 1 (Fombonne & Tidmarsh, 2003). Most studies suggest that prevalence does not vary according to racial or socioeconomic stratifications (Yeargin-Allsopp et al., 2003). Prevalence rates of ASD have increased in recent years, though inconsistency in diagnostic criteria used over time and across studies has complicated epidemiological studies (Ehlers & Gillberg, 1993). Fombonne (2005) reviewed epidemiological studies of autism spectrum disorders and found prevalence rates for autistic disorder ranging from 0.7 to 72.6 per 10,000, with the smallest sample sizes resulting in the highest estimates (and see Chapter 1.1). Fombonne calculated a conservative prevalence estimate for autism spectrum disorders to be 36.4 per 10,000; his best estimate of the prevalence rate for autism spectrum disorders was 60 per 10,000. Another recent study meta-analyzed prevalence studies and calculated a lower prevalence rate of 20 per 10,000 for autism spectrum disorders (Williams et al. 2006). Fombonne & Tidmarsh (2003) reviewed epidemiological studies of AS and found prevalence rates ranging from 0.3 to 48.4 per 10,000; statistically and theoretically accounting for measurement error and variation among studies, the authors suggested a working prevalence rate of 2.6 per 10,000 for AS. The Centers for Disease Control reported a prevalence rate of ASD of 1 in 150 children in 2007 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators, 2007) and 1 in 110 in 2009 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators, 2009). Though prevalence estimates have drastically increased in recent years, limited evidence indicates an actual change in the incidence of autism. Factors speculated to contribute to this increase in prevalence include increased awareness, more accurate recognition of higher- and lower-functioning ends of the autism spectrum, diagnostic substitution, and the influence of cultural, political, and legal factors, such as public perception and access to services (King & Bearman, 2009).

Comorbidity

AS commonly co-occurs with depression and anxiety, with estimates of comorbidity as high as 65 percent. The common overlap between AS and these mood disorders
has been posited to represent a potential distinction between AS and other high-functioning forms of ASD (Ellis et al., 1994; Fujikawa et al., 1987; Ghaziuddin et al., 1998; 2002; Green et al., 2000; Howlin & Goode, 1998). However, such discrepancies between AS and other ASD are not universally observed (Kim et al., 2000). Anxiety in AS may stem from several sources. Concern about possible violations of rigid routines or rituals can be anxiety-provoking for children with AS. They frequently rely on particular schedules or methods of completing daily activities that, when violated, result in significant distress. Conversely, when placed in a context in which no clear schedule or set of expectations is known, anxiety may result. Anxiety in individuals with AS may also manifest similarly to social anxiety, i.e., a preoccupation with failing during social encounters. Depressive symptomatology may also result from chronic frustration with social and romantic failures. Individuals with AS may become isolated over time, further increasing risks for anxiety and depression. In younger children, bullying is noted to contribute to isolation (Greenway, 2000; Mitchel et al., 2010; Sofronoff et al., 2011). Ironically, strong language abilities may render developmental difficulties less obvious and

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Social impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor nonverbal communication</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor empathy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Failure to develop friendships</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(implied)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Language/communication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor prosody and pragmatics</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Idiosyncratic language</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Yes</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Impoverished imaginative play</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>All-absorbing interest</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Often</td>
<td></td>
</tr>
<tr>
<td>Motor clumsiness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>Often</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset (0–3 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speech delays/deviance</td>
<td>No</td>
<td>May be present</td>
<td>May be present</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cognitive delays</td>
<td>No</td>
<td>May be present</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Motor delays</td>
<td>Yes</td>
<td>Sometimes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>May be present</td>
<td></td>
</tr>
<tr>
<td>Exclusion of autism</td>
<td>Yes (1979)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>No</td>
<td>May be present</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

ETIOLOGY AND PATHOPHYSIOLOGY

Biological Factors

Medical conditions have been associated with AS and have appeared in a number of case reports and small studies, but none have been reliably associated with AS across studies. Wing (1981) reported a high frequency of perinatal problems in the sample of individuals with AS that she described. Other reports have associated AS with medical conditions, including aminoaciduria (Miles & Capelle, 1987) and ligamentous laxity (Tantam et al., 1990). In a case series, Gillberg (1989) reported high frequencies of medical anomalies common to both AS and autism, but these results have not been consistently replicated (Rutter et al., 1994). Epilepsy occurs more frequently in individuals with ASD than in the general population (Tuchman & Rapin, 2002), including AS (Cederlund & Gillberg, 2004). Anomalies have also been detected in eye movements and visual scanning in individuals with ASD (Sweeney et al., 2004), particularly when viewing social scenes (Klin et al., 2005), but these findings do not distinguish AS from other ASD. Neurochemical studies of autism spectrum disorders have produced inconsistent results. The most robust finding is elevated blood serotonin levels, but other studies have reported atypicalities in peptide excretion, neuroendocrine/hypothalamic–pituitary–adrenal axis function, amino acid levels, uric acid excretion, and central cholinergic and GABAergic receptors; these findings have not been indicated to apply differentially to AS versus other ASD (Anderson & Hoshino, 2005).

In recent years, extensive neuroimaging research has been conducted, to investigate structural anomalies in the brains of individuals with AS. However, no clear common pathology has emerged in individuals with AS, either with respect to typical individuals or in terms of differentiation from other ASD. Berther and colleagues (1990) reported (MRI) results indicating left frontal macrogyria and bilateral opercular polymicrogyria in patients with AS. Other studies have reported gray tissue anomalies (McAlonan et al., 2002; Kwon et al., 2004), left temporal lobe damage (Jones & Kerwin, 1990), left occipital hypoperfusion (Ozbayrak et al., 1991), and dysmorphology superior to the ascending ramus of the Sylvian fissure proximal to the intersection of the middle frontal gyrus and the precentral sulcus (Volkmar et al., 1996). Functional imaging suggests abnormalities in brain activity associated with face-processing mechanisms in the inferotemporal cortex in ASD (Dawson et al., 2005; Schultz, 2005), and some of these anomalies have been specifically replicated in subsamples of individuals with AS (O’Connor et al., 2005). SPECT imaging suggests abnormal right hemisphere functioning in AS (McKelvey et al., 1995). Dysfunction has also been observed in brain regions subserving social cognition in AS, e.g., anterior cingulate cortex, prefrontal cortex, temporoparietal junction, amygdala, and periamygdaloid cortex (Schultz & Robins, 2005). An emerging body of research suggests problems with functional connectivity among separate brain regions in ASD (Just et al., 2004) and, specifically, in AS (Welchew et al., 2005). Despite these isolated examples of AS-specific brain differences, a recent review of 208 imaging studies failed to reveal robust differences between individuals with AS and other autism spectrum disorders (Pina-Camacho et al., 2011). Current brain imaging research fails to present a clear picture of the specific neurobiological underpinnings of AS or factors that distinguish it from other autism spectrum disorders.

Genetic Factors

Asperger’s original account described common symptoms in family members, especially fathers, an observation borne out in subsequent research. Overall, ASD are among the most heritable of psychiatric conditions, although the genetic etiology and pattern of heritability is still poorly understood. Many case reports have reported AS, ASD, or autistic-like traits in family members, particularly among fathers (Bowman, 1988; DeLong & Dwyer, 1988; Ghaziuddin, 2005; Gillberg & Cederlund, 2005; Gillberg et al., 1992; Volkmar et al., 1996; Wolff & McGuire, 1995), and recurrence rate in siblings of children with an ASD is considerably higher than the population base rate (Rutter, 2000). Some family history studies have also indicated associations with other psychiatric disorders including depression, schizophrenia, and schizoid personality disorders (Ghaziuddin et al., 1993). Klin and colleagues (2005) reported rates of ASD or the broader autism phenotype in parents and grandparents, including both males and females, of probands with AS were triple the rate found for the same relatives of probands with high
functioning autism (HFA; 17% vs. 5%). Nevertheless, the preponderance of research suggests shared genetic mechanisms common to all ASD (Frith, 2004). Some studies have reported specific genetic abnormalities in case studies of patients with AS: translocations, balanced translocations, and de novo translocations (chromosomes 1, 5, 11, 13, 14, 15, 17; Anneren et al., 1995; Cederlund & Gillberg, 2004; Tentler et al., 2001; 2003), autosomal fragile site (Saliba & Griffiths, 1990), fragile X syndrome (Bartolucci & Szatmari, 1987), fragile Y, and 21p+ (Cederlund & Gillberg, 2004; and see Chapter 2.1). Though numerous environmental factors have been postulated to interact with genes to play an etiological role in ASD, research has not shown consistent correlations (Wing & Potter, 2002).

Psychological Factors

Several studies suggest a distinct neuropsychological profile in AS (Lincoln et al., 1998). Klin and colleagues (1995) compared individuals with AS to those with other high-functioning autism spectrum disorders on a variety of neuropsychological measures, and determined that individuals with AS exhibited deficits in fine and gross motor skills, visual motor integration, visual–spatial perception, nonverbal concept formation, and visual memory with preserved articulation, verbal output, auditory perception, vocabulary, and verbal memory. Individuals with AS have been reported to exhibit stronger verbal abilities relative to performance abilities, with particular weakness in visual–spatial organization and graphomotor skills (Ehlers et al., 1997; Ghaziuddin & Mountain-Kimchi, 2004; Rourke, 1989). Overall, individuals with AS tend to demonstrate higher scores on measures of verbal functioning relative to individuals with autism (Reitzel & Szatmari, 2003). However, this study also found that individuals with AS did not consistently demonstrate nonverbal weaknesses or increased spatial or motor problems relative to individuals with HFA. Concordant with this finding, some researchers have argued that individuals with AS evidence overall greater cognitive ability than individuals with HFA, irrespective of verbal versus nonverbal ability (Miller & Ozonoff, 2000). Resolution of this issue is complicated by the employment of heterogeneous diagnostic schemes, which have been shown to directly influence IQ differential (Klin et al., 2005b).

ASSESSMENT

Diagnostic Assessment

Diagnostic assessment of AS is made according to clinical observation of the symptoms represented in ICD-10 or DSM-IV-TR criteria. Children thought to be at risk for AS should be referred for a multidisciplinary assessment by a team with specific experience in the assessment of ASD (Klin et al., 2005c). This practice ensures that complementary disciplines are employed to differentiate ASD from disorders with overlapping symptoms, such as expressive language disorder. Interdisciplinary assessment should entail thorough developmental and health history and include the disciplines of psychology, speech, and medicine. Depending on the age of the patient and presenting concerns, specialists in the areas of motor function (e.g., occupational or physical therapists), behavior modification, neurology, psychopharmacology, academic preparation, or vocational training should be consulted in the context of the evaluation.

Rigorous assessment for AS entails parent interview, direct observation of the individual, and psychological and speech and language assessment. Parent interview should inquire about social and communicative functioning, especially in the context of peer and romantic relationships, interests and hobbies, recreational activities, insight into the perspectives of others (including the impact of one’s own behavior on others), comprehension of figurative language, insight into the nature of social relationships and emotional experiences, and presence of repetitive and stereotyped behaviors and interests. Because individuals with AS may under-report or misperceive the status of social relationships, accounts should be verified independently by parents, educators, or individuals familiar with daily functioning. Given high comorbidity of anxiety and depression, mood symptoms should also be evaluated, as well as mental health status, including integrity of thought processes. The interview should include a thorough developmental history, emphasizing early social development to confirm stability of symptoms from early childhood forward.

Observation should directly assess social and communicative behavior through play- or interview-based methods, also monitoring atypical behaviors (e.g., motor mannerisms, sensory behaviors) or rigid or repetitive interests or behavioral routines. It is helpful to observe a person in both structured and unstructured contexts, as individuals with AS often display more normative behavior in highly structured or routine interactions. Social difficulties are most evident when predictability is reduced and scaffolding is not provided.

Psychological assessment should assess cognitive (or developmental) function, motor control, and adaptive functioning (Klin et al., 2007). Psychological assessment of cognitive or developmental function provides a context within which to gauge social-communicative function and to facilitate differential diagnosis, for example, learning disabilities versus AS. Speech and language assessment should measure language production,
language comprehension, nonverbal communication and gesture (including gaze and joint attention in young children), pragmatic and figurative language, prosody, rhythm, volume, and content of speech (Paul, 2005).

In addition to these discipline-specific assessments, formal diagnostic evaluation should also be included using standardized diagnostic assessments. Standardized self-report, parent/teacher report, and direct observation measures have been developed to screen for and diagnose AS and the other ASD. Though many are effective for this purpose, none to date reliably distinguish among individual ASD, such as discriminating Asperger syndrome from autistic disorder (Campbell, 2005; Lord & Corsello, 2005). The current ‘gold standard’ diagnostic protocol for ASD consists of a parent interview, the Autism Diagnostic Interview-Revised (Lord et al., 1994), and a semi-structured conversation/play-based interview, the Autism Diagnostic Observation Schedule (Lord et al., 2000). Both instruments require specific training to administer and score reliably. Differential diagnosis among ASD continues to rely on the judgment of experienced clinicians.

Additional Assessments

Genetic screening for various inherited metabolic disturbances is best practice, given increasing evidence for links between ASD and genetic syndromes with potential medical sequelae or for the relevance of genetic counseling. Genetic testing should assess for conditions known to cause ASD, such as fragile X syndrome, or inherited disorders that may have broader impact on physical health, such as phenylketonuria. Audiological evaluation is indicated to rule out contribution of auditory dysfunction to social and language impairments; brain stem auditory evoked response can be applied for individuals unable to comply with other methods of audiological assessment. Neurological consultation is appropriate if seizure activity is suspected, if late onset is observed, or if other indications of gross neurological dysfunction or soft signs are observed. Electroencephalograms (EEGs) and brain imaging, such as sMRI, are not recommended in all cases as they are neither diagnostic nor prescriptive; they may, however, be appropriate when concurrent non-ASD brain dysfunction is suspected (Minshew et al., 2005).

**TREATMENT, INTERVENTIONS, AND OUTCOME**

Treatment Objectives

Treatment for AS focuses on the development of age-appropriate social and communicative abilities, and aims to teach skills that are not naturally acquired during development by explicit instruction. Aside from considerations relevant to linguistic capability, verbal strengths, or nonverbal vulnerabilities, comparable treatment guidelines apply to AS and other high-functioning ASD (Mesibov, 1992). Limited data exist to support efficacy of particular interventions, although some progress has been made in this area (Klin & Volkmar, 2003). Recommended interventions focus on: (a) devising strategies to capitalize upon strengths (e.g., cognitive or memory skills) to compensate for areas of difficulty and (b) modifying environments to provide optimal support for learning and socialization. Intervention programs should be tailored to the individual needs of the child, based on a thorough multidisciplinary assessment as described above. Nearly all intervention programs will include acquisition of basic social and communication skills (especially pragmatic communication), adaptive functioning, and, depending on what is developmentally appropriate, academic or vocational skills (Attwood, 2000; Howlin, 1999; Myles & Simpson, 1997; Ozonoff et al., 2002).

When challenging behaviors, such as aggression, are present in individuals with AS, it is important to address the communicative intent of the behavior through functional behavior analysis and to develop a behavioral program to reduce its frequency. For older children and adults with AS, vocational training is important to teach appropriate etiquette for job interviews and workplace behavior. Explicit teaching and rote learning using a parts-to-whole approach is recommended (Klin et al., 2005c). Motor difficulties also require support and can be addressed with occupational therapies focusing on integration of learning in areas of weakness such as visual–spatial organization and body awareness. Intervention must also incorporate techniques to encourage generalization of acquired skills beyond the context of instruction.

**Psycho-Educational Interventions**

Many interventions capitalize upon strong language skills and a concrete cognitive style by establishing straightforward rules to guide behavior and teaching explicit verbal scripts to apply in social settings. These rules can be memorized and then practiced, first in therapeutic settings and then in more naturalistic settings. The focus on generalization has been repeatedly emphasized (Lee & Park, 2007) given the frequent tendency of individuals to be rigid and overly focused. Adopting explicit problem-solving strategies such as rules, scripts and ‘self-talk’ can be helpful. Assistive technology, such as organization software and personal data assistants, is a useful tool for supporting organization and work and
life management in individuals with AS (Ozonoff, 1998). Similarly, specialists in communication can help to foster pragmatic language abilities in areas like self-monitoring, topic management, turn taking, conversational rules, speech volume, and prosody (Paul et al., 2009).

A recommended treatment modality for children with AS is social skills groups, as they provide a forum in which children can learn skills, practice them, and be coached and reinforced in vivo. Social skills groups can foster social skills and offer explicit teaching of conversational rules and interactional strategies (Kaland et al., 2011; Rubin & Lennon, 2004; Saulnier & Klin, 2007). Such settings facilitate targeting of both social motivation for peer connection and improve verbal and rote memory abilities (Beaumont & Sofronoff, 2008; Macintosh & Dissanayake, 2006; Muller, 2010; Patrick, 2008). Psychotherapy using a more problem-oriented ‘life-coaching’ approach can also be productive (Mero, 2002; Munro, 2010; Volkmar, 2011), and increasing evidence supports the effectiveness of cognitive behavioral therapies for AS (Cardaciotto and Herbert, 2004; Weiss & Lusky, 2010).

Pharmacological Interventions

Drug treatments that specifically target the core social vulnerability of AS have not yet been established. However, pharmacological interventions have an important place in the treatment of the frequent comorbid conditions, particularly inattention in younger children and anxiety and/or depression in adolescents and adults (Gutkovich et al., 2007; Tsai, 2007; Volkmar & Wiesner, 2009). As is the case for psychological and educational interventions, most available literature comes from case reports or open clinical trials rather than rigorously controlled studies. It is not uncommon for younger children with AS to be given trials of stimulant medications, often prior to receiving an accurate AS diagnosis (Ehlers et al., 1997).

DEVELOPMENTAL COURSE AND OUTCOME

Direct comparisons to other ASD are intrinsically complex, given the preserved language skills in AS (Gilchrist et al., 2001; Howlin, 2003; 2005; Szatmari, 2000). Asperger’s observation of similar problems in parents suggested a more positive long-term outcome in that these individuals had maintained gainful employment and raised families. Research on long-term outcomes in AS, as in other areas, is complicated by differences in overall diagnostic approach but, in general, the data suggest that relative to both classical autism (Gillberg, 1991) and more narrowly defined high-functioning autism (Gillberg, 1998), the outcome is more positive overall. However, research using divergent definitional approaches yields mixed results (Szatmari et al., 1989). Several factors may contribute to better outcome, including the impact of overall cognitive abilities and particularly good verbal abilities, as well as associated capacities for developing coping strategies and finding suitable employment. Many individuals with AS continue to have significant needs and some remain at home with few occupational opportunities (Gillberg, 1998; Howlin, 2004; 2005; Tantam, 1991). Even when overall cognitive abilities are greater, adaptive skills deficits may present a major challenge for personal independence and self-sufficiency (Saulnier & Klin, 2007). Acquisition of adaptive skills is a critical factor in predicting longer-term outcome (Szatmari et al., 2003).

FUTURE DIRECTIONS

Though excellent progress has been made since Wing (1981) brought AS to the world’s attention, the disorder remains incompletely understood in several important regards. Additional nosological study is needed to validate the diagnostic construct as distinct from other autism spectrum disorders and to increase reliability in diagnosis of AS among raters (Lord et al., 2011). This could support development of standardized diagnostic tools sufficiently sensitive to reliably discriminate. Along these lines, it remains to be clarified to what extent distinct educational and social/behavioral approaches are most appropriate for AS versus other ASD. Though pharmacotherapy is a promising treatment approach, additional work must be done to develop recommendations for specific medications to treat specific symptoms with an eye towards long-term efficacy and potential side effects. Ongoing work in neuroscience and genetics, and the integration of these fields, may provide evidence for biologically based screening instruments and biologically informed medical treatments. Despite the progress made in understanding AS and its place in the broader autism spectrum, the future of AS as a psychiatric diagnosis is unclear. The release of the DSM-5, anticipated in 2013, proposes diagnostic criteria to collapse AS, as well as the autistic disorder and PDD-NOS, into a single broad category of ASD. Relative to other psychiatric disorders, AS has been intensively studied for a short period of time; nevertheless, it may soon cease to exist.

References


1. AUTISM SPECTRUM DISORDERS
REFERENCES


1. AUTISM SPECTRUM DISORDERS


