**Autism Spectrum Disorder**

**JC McPartland and K Law,** Yale Child Study Center, New Haven, CT, USA
**G Dawson,** Duke University School of Medicine, Durham, NC, USA

© 2016 Elsevier Inc. All rights reserved.

### Glossary

**Applied behavior analysis** A category of intervention approach for ASD based on principles of reinforcing desired behaviors to effect behavior change, usually improvement in social-communication skills. Examples include Discrete Trial Intervention, Pivotal Response Training, and the Early Start Denver Model.

**Asperger’s disorder** A neurodevelopmental disorder characterized by impairments in social communication and restricted, repetitive behaviors, and without clinically significant delays in language or cognitive development. Asperger’s disorder was not continued as a diagnostic category in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders.*

**Autism spectrum disorder (ASD)** A neurodevelopmental disorder characterized by difficulties in social communication and the presence of restricted, repetitive behaviors and atypical sensory behavior. As of DSM-5, ASD includes the former categories of autistic disorder, Asperger’s disorder, and pervasive developmental disorder – not otherwise specified.

**Autistic disorder** A neurodevelopmental disorder characterized by significant difficulties in social behavior, communication, and the presence of restricted, repetitive behaviors. Autistic disorder was not continued as a diagnostic category in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders.*

**Pervasive developmental disorder – not otherwise specified (PDD-NOS)** A neurodevelopmental disorder characterized by milder or fewer symptoms than would meet diagnostic criteria for autistic disorder or Asperger’s disorder. PDD-NOS was not continued as a diagnostic category in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders.*

**Social (pragmatic) communication disorder** A communication disorder characterized by difficulties in social communication, without the presence of restricted, repetitive behaviors.

### Introduction

Autism Spectrum Disorder (ASD) is an early onset, pervasive, and lifelong neurodevelopmental disorder characterized by challenges in social communication and repetitive, restricted behavior patterns and atypical response to sensory stimuli. Since the first published description of autism (Kanner, 1943), estimates of prevalence have dramatically increased, with current estimates indicating 1 in 68 individuals in the United States are diagnosed with ASD. Although biases in access to care may exist, ASD is evident in all racial, ethnic, and socioeconomic groups (Centers for Disease Control (CDC), 2014).

### Clinical Characteristics

Autism is currently conceptualized as a spectrum disorder, reflecting significant phenotypic and genotypic heterogeneity (Abrahams and Geschwind, 2008), including considerable variability in intellectual and communicative ability. Its developmental impact is pervasive, spanning multiple domains of function and leading to impairment in multiple aspects of adaptive functioning. Individuals with ASD require various levels of support with their daily living, ranging from needing continual care to being fully independent. The unifying diagnostic features of ASD are persistent impairments in social communication and restricted, repetitive behaviors and atypical sensory behavior.

### Social Communication

Individuals with autism display deficits in (1) socio-emotional reciprocity. They may seem to lack interest in or struggle with sustained social interactions. For example, they may be unable to initiate conversation or may have one-way conversations about topics of their own interest. They also demonstrate (2) deficits in nonverbal communication. For example, they may have poor eye contact or difficulty understanding body language and facial expressions. In addition, individuals with autism (3) have difficulty maintaining relationships. For example, they may seem to lack interest in making friends or have difficulty adjusting their behaviors to match different social situations (American Psychiatric Association (APA), 2013).

### Restricted, Repetitive Behavior

Individuals with ASD also demonstrate at least two patterns of restricted, repetitive behaviors. They may (1) have repetitive movements or language, such as lining up toys or repeating a phrase at unusual times. Alternatively, they may (2) display behavioral rigidity such as experiencing extreme distress to small changes. Furthermore, individuals with autism may (3) have restricted interests that are abnormal in intensity or focus. Additionally, they may (4) display unusual sensory reactivity. For example, they may strongly attempt to avoid specific textures and sounds, or appear indifferent to physical pain (APA, 2013).
Other Clinical Features

Finally, in order to receive a diagnosis of autism, behaviors must not be primarily explained by intellectual disability or global developmental delay; however, associated intellectual disability is common (APA, 2013). Individuals with autism also have elevated comorbidities with other psychiatric disorders such as attention deficit hyperactivity disorder, depression, and anxiety (White et al., 2009; APA, 2013), as well as other medical conditions, such as seizures and gastrointestinal problems (Volkmar and Nelson, 1990; McPartland and Dawson, 2014). Other common features of ASD that are not required for diagnosis include motor deficits, self-injurious behaviors, and catatonia (APA, 2013).

Developmental Course

Autism can have an early onset, in which symptoms of autism are apparent shortly after birth, or a late onset, in which typical development is followed by stagnation in development or regression of skills (APA, 2013). In the first months of life, infants who later receive an ASD diagnosis begin to diverge in their reduced attention to social stimuli compared to typically developing infants (Chawarska et al., 2013). Symptoms of ASD must be present in early development and reliable diagnoses can be determined as early as 2 years of age (Lord et al., 2006), although average age of diagnosis is closer to 4 years of age (CDC, 2014). Individuals with autism are typically able to learn throughout their lifetime, and many individuals make remarkable developmental gains with appropriate treatment. The absence of associated intellectual disability and the presence of stronger verbal language ability have been associated with better prognosis (Hus et al., 2012; APA, 2013). Some individuals experience skill deterioration in adolescence and very little is known about outcomes in old age (APA, 2013).

Etiology

Research suggests that autism is caused by a combination of both genetic and environmental risk factors. Family studies have shown that there is a strong genetic component to the etiology of idiopathic autism. For monozygotic twins, if one twin has autism, the other twin has autism 36–95% of the time; meanwhile, the concordance rate for dizygotic twins is lower, at around 31% of the time (Hallmayer et al., 2011; Ronald et al., 2006; Rosenberg et al., 2009; Taniai et al., 2008). For siblings, if one sibling has autism, the reoccurrence rate for siblings is around 10–18% (Ozonoff et al., 2011; Sumi et al., 2006). Relatives of an individual with ASD are also more likely to share a broad autism phenotype, including characteristics such as social rigidity and elevated rates of language impairment (Losh et al., 2008). For example, siblings of individuals with autism are more similar than typically developing peers to their affected siblings in measures of IQ and adaptive functioning (Goin-Kochel et al., 2008). These results indicate that the more genetically similar individuals are to a family member with ASD, the more likely they will also have a diagnosis of ASD or autistic-like traits. In addition, several genetic subgroups of autism have been identified (Abrahams and Geschwind, 2008). Yet, even monozygotic twins, which have the most genetic similarity, do not have a 100% concordance rate of autism, indicating that there are environmental influences on the disorder as well. Recent research has identified a number of potential environmental risk factors for autism, such as exposure to air pollution, pesticides (Shelton et al., 2014), and certain medications during the prenatal period (Croen et al., 2011). Advanced parental age at conception has also been associated with increased risk for autism (Hultman et al., 2011).

Diagnostic Evolution of Autism Spectrum Disorder

To establish a differential diagnosis of autism, clinicians in the United States primarily refer to the guidelines in the fifth edition of Diagnostic and Statistical Manual for Mental Disorders (DSM-5). The DSM-5 was published in May 2013 (APA, 2013) and replaced the guidelines of the previous DSM-IV, which had been used in clinical and research settings for over a decade (APA, 2000). Potential implications of these diagnostic changes have been discussed widely since publication and in the years preceding this revision. Below, we review the specific changes in diagnostic criteria, and their implications with respect to sense of self, stigma, and access to services (Volkmar and McPartland, 2014; McPartland and Dawson, 2014).

Diagnostic and Statistical Manual for Mental Disorders-IV

Diagnostic Criteria

Prior to the DSM-5, the DSM-IV categorized autism into three distinct diagnostic subgroups: (1) autistic disorder, (2) Asperger’s disorder, and (3) pervasive developmental disorder – not otherwise specified (PDD-NOS) (APA, 2000). A diagnosis of autistic disorder was characterized by the most severe symptomatology, requiring a total of six symptoms before age 3, from three diagnostic domains: (1) impairment in social interaction (at least two symptoms), (2) impairment in communication (at least one symptom), and (3) the presence of restricted, repetitive behaviors (at least one symptom). In contrast, Asperger’s disorder was characterized by no clinically significant delay in language or cognitive development, but having at least two symptoms of impaired social interaction and at least one symptom of restricted, repetitive behaviors. Finally, PDD-NOS was a ‘sub-threshold’ diagnosis given to individuals who did not meet criteria for autistic disorder or Asperger’s disorder, but had significant impairments in comparable diagnostic domains (APA, 2000).

Changes in the Diagnostic and Statistical Manual for Mental Disorders-5

In the DSM-5, the diagnostic subgroups of autistic disorder, Asperger’s disorder, and PDD-NOS have been merged into one diagnostic category of ASD (APA, 2013). The merging of these subgroups in the DSM-5 supports the emerging conceptualization of ASD as a continuum of behaviors and corresponding biological factors. Furthermore, the previous subgroups were subject to clinician-related factors and not reliably applied (Lord et al., 2012a; McPartland and Dawson, 2014).
In addition to merging the diagnostic subgroups of autism, the DSM-5 has merged the previous DSM-IV social and communication diagnostic subdomains into one diagnostic subdomain of impairments in social communication. Furthermore, the DSM-5 requires an individual to exhibit a symptom in every symptom cluster of the social communication subdomain to meet criteria for ASD diagnosis. This system differs from the polythetic DSM-IV, in which a combination of symptoms in various clusters would qualify for diagnosis (McPartland and Dawson, 2014; Volkmar and McPartland, 2014). Therefore, there were 2207 possible symptom combinations that would have met criteria for autistic disorder under the DSM-IV, yet only 11 combinations of criteria for a diagnosis of ASD under the DSM-5 (McPartland et al., 2012).

Restricted and repetitive behaviors remain a separate subdomain in the DSM-5, and diagnosis does not require symptoms from all clusters to be present. However, the DSM-5 requires symptoms in at least two symptom clusters, whereas the DSM-IV only required symptoms in one cluster within this subdomain. In addition, unusual sensory processing is a new symptom cluster only recognized in the DSM-5 as a common symptom, though not required for diagnosis (APA, 2000, 2013).

For each subdomain of ASD in the DSM-5, a new severity level is required for the recording process. Severity levels range from Level 1 (‘Requiring support’), Level 2 (‘Requiring substantial support’), to Level 3 (‘Requiring very substantial support’) (APA, 2013). Additionally, for the first time, the DSM-5 acknowledges culture- and gender-related diagnostic issues. For example, the DSM-5 specifies the level of impairment observed must be compared to the norms of the individual’s culture. Furthermore, the DSM-5 cautions that females without accompanying intellectual impairment or language delays may have subtler social communication difficulties that have been more likely to escape detection (APA, 2013).

Some individuals with ASD-like symptoms may now be diagnosed under a new diagnostic category of social (pragmatic) communication disorder (SCD), which characterizes individuals with difficulties in social communication who do not have restricted, repetitive behaviors. A diagnosis of ASD precludes a diagnosis of SCD, although ASD can be a familial risk factor (APA, 2013; McPartland and Dawson, 2014). A key difference between ASD and SCD is that SCD is classified as a communication disorder. The educational supports and insurance coverage granted for communication disorders may be less inclusive than for ASD, thereby limiting resources for individuals diagnosed under the new SCD category. For instance, individuals with ASD are more likely to receive a variety of intensive behavioral interventions, while individuals with a communication disorder are more likely to only receive speech therapy (Grant and Nozyce, 2013). In addition, since SCD is a novel diagnostic category, empirically validated assessments and treatments for SCD do not exist yet. Therefore, until SCD is better understood, individuals with SCD may still benefit from treatments developed for ASD (McPartland and Dawson, 2014).

**Implications of diagnostic changes**

DSM-5 criteria have been interpreted as potentially more restrictive than DSM-IV criteria (Volkmar and Reichow, 2013). Early reports suggested that individuals with milder forms of DSM-IV spectrum diagnoses, such as Asperger’s disorder and PDD-NOS, and individuals with normative cognitive abilities, are more likely to be excluded from an ASD diagnosis under DSM-5 criteria (McPartland et al., 2012). It has been proposed that individuals meeting DSM-5 criteria might be more impaired than those meeting DSM-IV-TR criteria (Worley and Matson, 2012; Matson et al., 2012). Other studies have suggested that DSM-5 criteria were less sensitive in detecting females (Frazier et al., 2012) and very young children (Barton et al., 2013). However, in a large multisite study, DSM-5 criteria were highly sensitive (~91%) and corresponded closely to DSM-IV-TR criteria (Huerta et al., 2012). Studies to date have limitations and significant methodological variability in data collection and symptom endorsement, factors recognized to influence ascertainment (Mazefsky et al., 2013). Studies comparing diagnostic rubrics in a prospective manner are now in progress and are necessary for accurate estimation of the effects of DSM-5 on the prevalence of ASD. Importantly, individuals with an established DSM-IV diagnosis of autistic disorder, Asperger’s disorder, or PDD-NOS will retain their diagnosis in the DSM-5 (APA, 2013). Therefore, these diagnostic criteria changes will only affect newly diagnosed individuals.

Another critical issue will be revision of ‘gold standard’ autism diagnostic assessments based on DSM-IV diagnostic standards. For example, in 2012, the Autism Diagnostic Observation Schedule (ADOS) underwent revision (ADOS-2) in preparation for the then-proposed revisions to the DSM-5. Parallel to changes from the DSM-IV to DSM-5, the ADOS-2 added a classifier of symptom severity, and also merged communication and social subdomains into one subdomain of social communication (Lord, 2002; Lord et al., 2012b). The Autism Diagnostic Interview – Revised (ADI-R) has not yet been revised since the DSM-5 was published (Rutter et al., 2003). At present, the field’s best diagnostic instruments may lack correspondence to one another and to current diagnostic criteria.

Taken together diagnostic changes appear to increase the specificity of correctly identifying those with ASD, a needed advance for diagnosed individuals receiving specific, appropriate supports. In addition, improved phenotypic and genotypic homogeneity will hopefully improve the ability of researchers to detect studied effects in the long term. However, potentially decreased sensitivity to diagnosing higher functioning individuals on the spectrum may result in decreased access to services for some individuals. Finally, the large amount of autism research conducted in the past decades will no longer directly correlate to new DSM-5 standards (McPartland and Dawson, 2014). Although appreciable changes may be minimal (Huerta et al., 2012), these unprecedented issues should still be carefully considered in planning future research and clinical practice.

**Sex Differences in Autism Spectrum Disorder**

Autism occurs in males almost five times more than females. For this reason, most research to date has focused primarily on males with ASD. Early studies of sex differences in ASD did not
consistently control for IQ, sample size, and lacked decisional consensus. In recent years, the import of studying sex differences in ASD has been increasingly recognized.

**Behavioral and cognitive characteristics**

While females and males do not significantly differ on most core autism symptomology, distinct profiles have been observed for associated features (Frazier et al., 2014). Overall, females tend to be more severely affected by ASD than males. More females tend to have IQs in the intellectually disabled range (Lord and Schopler, 1985; Volkmar et al., 1993). Females with ASD have more comorbidities with other psychopathologies, sleep problems, attention problems (Hartley and Sikora, 2009), and thought problems (Holtmann et al., 2007). They also tend to have more sensory issues (Lai et al., 2011), motor difficulties (Carter et al., 2007), irritability, lethargy, and self-injurious behaviors (Frazier et al., 2014).

Interestingly, females with high functioning autism initially show fewer social problems at young age (McLennan et al., 1993). However, by adolescence females with ASD tend to have more emotional difficulties (Holtmann et al., 2007), and have more profound social communication impairments and worse adaptive behavior (Mandy et al., 2012; Frazier et al., 2014). On the other hand, females tend to consistently have less restricted, repetitive behavior, and fewer interpersonal conflicts over time (Mandy et al., 2012; Coffman et al., 2013). These differences are important for recognizing and treating autism symptoms appropriately across the sexes, as diagnostic criteria and treatment development have mainly focused on symptoms as observed and measured in males.

**Biological characteristics**

In addition to studying behavioral and cognitive sex differences, biological studies can provide more objective, precise measures of sex differences. In a molecular study of individuals with Asperger’s disorder and typically developing controls, males and females with Asperger’s disorder showed distinct and atypical patterns of blood serum biomarkers. For example, males with Asperger’s disorder showed increased levels of cytokines and inflammatory molecules compared to females with Asperger’s disorder and all controls. In contrast, females with Asperger’s disorder showed increased levels of growth factors and hormones compared to males with Asperger’s disorder and all controls (Schwarz et al., 2010). Furthermore, neuroimaging studies have discovered differences in brain composition between males and females with ASD (Lai et al., 2013). For example, males with ASD had larger gray matter volume in the dorsomedial prefrontal cortices and females with ASD had larger gray matter volume in the left dorsolateral prefrontal cortex. Such findings indicate that the biological correlates of ASD symptomatology may differ between males and females. Complementing research on the biological state of individuals with ASD, other studies have focused on parsing the functional significance of these attributes. In an electrophysiological study of males and females with ASD, females showed reduced neural specialization (P100, N170) to social stimuli than males despite similar performance on adaptive social and communication skills and facial recognition. More atypical neural differentiation between social and nonsocial stimuli was correlated with higher levels of autistic symptomatology for females but not for males (Coffman et al., 2013). Altogether, these differences may implicate unique social processing mechanisms between males and females.

**Implications of sex differences in autism spectrum disorder**

As shown by behavioral and biological studies, individuals with ASD can vary notably by sex. It will be important for future research to plan samples such that stratification by sex is adequately powered. In addition, understanding sex-specific symptoms of autism is essential to ensuring females are not underdiagnosed in a diagnostic system predominantly based on male-centric symptoms. Furthermore, accompanying comorbidities more common in females may interfere with intervention strategies. Therefore, a greater understanding of biological mechanisms underlying sex differences may provide more precise treatment strategies and diagnostic procedures. Consequently, although the literature on sex differences in autism has been increasing, a tremendous amount of work still remains to be investigated.

**Neural Plasticity and Behavioral Treatment**

Behavioral treatments have been found to result in improved cognitive, language, and adaptive behavior, although the degree of improvement varies widely (Sullivan et al., 2014). Some individuals make remarkable gains with treatment. In contrast, some individuals make much slower gains and a substantial subgroup remains minimally verbal (APA, 2013).

While there are many behavioral treatment models for autism, evidence-based and efficacious treatments share common themes. The foundation of most behavioral treatments is building (1) supportive environments that provide ample opportunities for learning social, cognitive, and language skills. During the preschool years, these interventions have predictability and year-round active engagement around at least 25 h a week. For example, one-on-one attention or very small group instruction is common between students and teachers (Dawson and Osterling, 1997; National Academy of Sciences-National Research Council, 2001). Furthermore, (2) early intervention is a goal of many treatment programs. In addition, (3) individualized, (4) functional curriculums (i.e., focusing on developmentally appropriate skills) with (5) generalization strategies predict greater success outside of the classroom (Dawson and Osterling, 1997; National Academy of Sciences-National Research Council, 2001; Wallace and Rogers, 2010). Current early intervention models use naturalistic developmental behavioral approaches. Examples include pivotal response treatment (PRT), which expanded principles of applied behavior analysis to target social skill acquisition across multiple cues of social reward rather than rote learning with nonsocial reward (Koegel et al., 2001), and the Early Start Denver Model (ESDM) has been developed for toddlers as young as 12 months old (Rogers and Dawson, 2010). Progress in treatments must be monitored with (6) ongoing evaluations to appropriately adjust treatment strategies. Finally, (7) family involvement is critical so that treatment gains are continued at home and through an individual’s lifetime, as he or she transitions through various programs.
Brain Changes with Treatment

Although treatments target behavioral outcomes, the biological mechanisms of treatment changes are less understood. However, emerging theories about brain change mechanisms and supporting evidence have begun to steer behavioral treatment designs.

Shaping brain connectivity with early intervention

Due to the relative enhancement of neural plasticity in infancy, early intervention has been a strong focus in the autism field. Infants and children with ASD commonly have an atypically rapid rate of brain growth in early life, followed by an accelerated decline (Courchesne et al., 2001). Early neuronal overgrowth can have widespread effects for the developing brain, including structural abnormalities, increased local connectivity, and reduced long-distance neuronal connectivity (Courchesne and Pierce, 2005; Wolff et al., 2012). These atypical brain changes can be seen behaviorally, as individuals with ASD have impaire performance on higher-order tasks that require long-distance neuronal connectivity, but perform as well or better than their typically developing peers on lower-order perceptual tasks that rely on local connectivity (Williams et al., 2006). Unmediated by treatment, these differences can lead to a developmental cascade of negative effects. For example, infants who focus on simple objects rather than complex social stimuli, may increasingly miss opportunities to specialize in social learning (Sullivan et al., 2014). Therefore, in order to facilitate specialization in social learning, treatments target increasing the salience of complex social stimuli for individuals with ASD. For example, children with ASD who started early intervention based on the ESDM intervention before 2.5 years showed normalized brain responses to social and nonsocial stimuli compared to children who did not receive ESDM (Dawson et al., 2012). In a pilot study, children who received PRT showed normalized brain activation in areas thought to influence executive decisions and facial recognition (Voos et al., 2013). These encouraging results demonstrate that the brains of individuals with ASD are malleable to treatment and able to approach more adaptive functioning.

Targeting neurotransmission imbalances

Other research suggests that ASD symptoms arise as a broader result of an imbalance between excitatory and inhibitory activity in cortical networks due to a reduction in GABAergic signaling (Rubenstein and Merzenich, 2003). Consistent with this hypothesis, children who received ESDM showed a normalization of inhibitory and excitatory neuronal balance, whereas children who did not receive ESDM showed an imbalance (Dawson et al., 2012). In addition, dysfunction in the dopaminergic system is hypothesized to influence atypical social motivation in ASD (Sullivan et al., 2014) and increased serotonin axons can be observed in postmortem brains of individuals with ASD (Azmitta et al., 2011). Monitoring these neurotransmitters provides potential novel measures of treatment sensitivity and progress, as well as targets for medicinal treatments.

Recommendations

Although the autism field has advanced dramatically in the past several decades, progress is required to develop appropriate individualized treatments that improve the lives of individuals with ASD by targeting specific mechanisms of impairment and bolster preserved or compensatory functions. Including health care, education, therapies, and caregiver supports, additional societal costs of caring for children with ASD is estimated to be over US$11 billion per year (Lavelle et al., 2014; Shimabukuro et al., 2008). Due to the heterogeneous complexity of autism, multidisciplinary studies with large samples are needed to efficiently understand autism across modalities. Furthermore, researchers and clinicians should be cognizant of the values and needs of individuals with ASD and their families to best design and share the importance of their work. An increasing recognition of neurodiversity has transitioned emphasis on a ‘cure’ to a perspective in which both the strengths and challenges of ASD are appreciated and therapeutic efforts are focused on remediating disability associated with ASD.

References


