Phenotypic Variability in Autism Spectrum Disorder: Clinical Considerations

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Introduction

The qualitative impairments in social-communicative behaviors and repetitive and restrictive behaviors and interests that define autism spectrum disorder (ASD) are known to be highly variable. This heterogeneity leads to important challenges for diagnosis and classification, epidemiology, treatment, and the understanding of pathogenesis. Major diagnostic systems attempt to allow for the variability, but it has proven challenging to find a systematic way of doing so. After all, it is a formidable task to find a set of criteria that reliably distinguishes a group of people who have different developmental levels. Rarely do two children with ASD present with identical symptoms, and factors such as developmental level, language ability, and intelligence quotient (IQ) further complicate the presentation of symptoms. Perhaps the most parsimonious way we currently have to decrease heterogeneity of the ASD phenotype is with level of intellectual functioning. This is certainly not a panacea and there are other ways this could be done, but IQ does help to decrease and/or explain phenotypic variability in ASD.

In this section, high- and low-functioning ASD are contrasted and discussed in terms of prevalence, etiology, diagnosis, clinical presentation, and outcome. It is important to note that high- and low-functioning ASD could be defined in several ways. Here, they are broadly defined as ASD with or without intellectual disability (ID), which is defined as an IQ below 70 in most writings. ID is a state of functioning characterized by intellectual and adaptive deficits with an onset in the developmental period. It is objectively defined, but the cutoffs used are arbitrary (AAIDD 2010; APA 2013). Even this artificial dichotomy might not be ideal as there are increased neurobiological abnormalities in people with IQs below 50 (Jacobson et al. 2007; van Bokhoven 2011). Furthermore, other proxies for cognitive ability such as adaptive behavior or language are sometimes used to define high and low functioning when discussing important clinical domains in people with ASD. Finally, sometimes the terms are only used to refer to a median split of the sample under study.

Prevalence

The topic of high- and low-functioning ASD is quite germane to the rise in prevalence observed in the past 40 years. Surveys have clearly shown that prevalence figures published after 2000 have yielded higher rates of case identification (Fombonne 2009). The change in our conceptualization of ASD to include children from all levels

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of functioning and those with other neuropsychiatric and medical disorders is one factor that has contributed to this increase. Recent surveys have suggested much higher rates of about 60–70/10,000 (Fombonne 2009). It is now believed that most children on the autism spectrum do not function in the range of ID. Indeed, approximately 40–50% fall in the ID range, although rates were higher for *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition's* (*DSM-IV*; APA 2000) autistic disorder, which by definition consisted of more symptoms than Asperger syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS). In autistic disorder, rates of ID have been reported to hover around 70%. They also clearly vary according to the level of intellectual deficits, with approximately 30% having mild-to-moderate impairments and 40% having severe-to-profound impairments (Fombonne 2009).

In addition to changes in our conceptualization and measurement of ASD, a number of policy changes have contributed to increased prevalence. The introduction of the 1990 Individuals with Disabilities Educational Act in the USA was followed by diagnostic practice changes, whereby children previously diagnosed with ID were being diagnosed with ASD, either with (accretion) or without (substitution) a co-occurring diagnosis of ID. There is evidence of simultaneous decreases in the population prevalence of ID along with increases in ASD (Shattuck 2006). In other words, some children who in the past would have received a diagnosis of ID have received an ASD diagnosis in more recent times when presenting with similar behaviors. Exactly how much of the increase is due to "diagnostic substitution" is not known. King and Bearman (2009) analyzed data from the California Department of Developmental Services database and found that children previously classified with "mental retardation" accounted for one-quarter of the measured increase in autism prevalence between 1992 and 2005. These definitional issues are reminiscent of the diagnostic substitutions between learning disability and mental retardation seen in the 1990s (*s*ee MacMillan and Speece 1999*)*.

In addition to policy changes, the epidemiology of ASD has been impacted by a number of social factors. For instance, Palmer et al. (2005) reported that the proportion of economically disadvantaged children per school district was inversely associated with the proportion of autism cases in the Texas Education Agency database. The prevalence estimate of autism for school districts in the top decile in terms of revenue was six times higher than for school districts in the bottom decile of revenue. In other words, children were more likely to be educationally classified as having autism if they were in a school district with more financial resources. The exact reasons for this are likely multiple, but the ability to navigate convoluted bureaucracies to be deemed eligible for services can impact identification rates and advantage families of higher socioeconomic status.

In summary, multiple factors have impacted the rise in ASD prevalence. Definitional changes and inconsistencies as well as changes in social policy have clearly impacted prevalence rates. These variables have impacted high- and low-functioning ASD differently, but the result is that more people are being diagnosed with ASD today than 20–30 years ago, and many of them are considered high-functioning individuals.

Etiology

The past 15 years have brought remarkable progress in the understanding of the etiology of ASD (e.g., Amaral et al. 2008; Ameis and Szatmari 2012; Dodds et al. 2011; Geschwind 2011; Grafodatskaya et al. 2010). One thing is clear: The etiology of ASD is multifactorial and complex. There are multiple genes and environmental factors that contribute to ASD susceptibility. Several lines of evidence suggest that epigenetics also plays an important role in the causes of ASD by integrating genetic and environmental influences to dysregulate neurodevelopmental processes. It is clear that ASD arises from many different etiologies and represents the final outcome of multiple pathological processes.

There is a complex relationship between ASD and ID. The strength and origin of the association remain unclear, but it is hoped that a better understanding of this relationship will lead to a better understanding of the etiology of ASD. On the one hand, the overlap between ASD and ID suggests genetic similarities. Indeed, genetic disorders that are characterized in part by ID, such as fragile X, tuberous sclerosis, or Smith–Lemli–Opitz syndrome, occur at substantially higher rates in individuals with ASD compared to the general population (e.g., Grafodatskaya et al. 2010; Geschwind 2011). We also know that copy number variations explain up to 10% of idiopathic ASD and are also implicated in ID. Such an overlap between ASD and ID argues for a search of common genes influencing both conditions. On the other hand, studies have also reported limited associations between ASD traits and IQ, suggesting separate genetic influences on specific traits. For instance, Hoekstra et al. (2009) reported on the association between autistic traits and ID in a population-based sample of twins between 7 and 9 years old. Only modest correlations were found between IQ and autistic traits (correlations between −.01 and −.40). The association was driven by communication problems characteristic of ASD and suggested that autistic traits are substantially genetically independent of ID. It could be that the genetic risks for ASD and ID are distinctly different, and it is the combination of these conditions that leads to a recognizable ASD. Skuse (2007) proposed that individuals who are genetically susceptible to ASD who also have adequate cognitive skills can compensate for the social-cognitive deficits that are associated with the genetic vulnerability toward ASD. Individuals with the same genetic risk for ASD who function at a lower level are more likely to develop an ASD due to the absence of protective cognitive skills and the increased likelihood of clinical identification.

One of the most well-established findings in the genetic epidemiology of ASD is the fourfold male predominance (Fombonne 2009). In addition, several studies have shown that when females are affected by ASD, they exhibit a more severe form of the disorder, at least when severity is defined in terms of lower IQ or adaptive functioning deficits. This has been clearly demonstrated in epidemiological studies which show that the gender ratio approaches equality at the level of severe ID, but has many more boys than girls in the normal IQ range. The reasons behind this relationship remain a mystery. It has been proposed that females at risk are protected in some way, so that only those with the greatest genetic liability are affected. The relationship between gender and IQ is likely muddled by other variables. For instance, Banach et al. (2009) compared 194 simplex and 154 multiplex families on measures of severity, including nonverbal IQ. Among simplex families (only one child with autism in the family), girls had lower nonverbal IQs than boys, but no such differences were seen among multiplex families (more than one child with autism in the family). Similarly, the affected brothers of girls with autism were no different from affected brothers of male probands. These data suggest that both simplex and multiplex families differ with respect to the relationship between gender and level of functioning.

A final word on etiology and its relationship to level of functioning: It is well-documented that people with ASD have higher rates of neurological problems such as cerebral palsy, microcephaly, and sleep disturbances. One of the more commonly reported co-occurring medical problems is epilepsy (Caniato 2007). Whereas the prevalence of epilepsy in the general population is between 0.5 and 1%, the prevalence in ASD is substantially higher with figures ranging from 5 to 40% (Caniato 2007). ID has been identified as one factor that may account for the variability in prevalence rates. Amiet et al. (2008) synthesized the literature on epilepsy and intellectual functioning in people with ASD in a meta-analysis. They found that the prevalence of epilepsy was higher in individuals with ASD and ID as compared to those without ID. Pooled prevalence rates indicated a rate of 21.4% for individuals with ASD and ID versus 8% in individuals with ASD without ID. Additionally, it was reported that within the sample of individuals with comorbid ID, the

prevalence of epilepsy increases with the severity of ID.

Diagnostic and Clinical Features

Level of functioning is associated with a host of clinical features. Related to this are a few general diagnostic issues that warrant consideration. First, level of functioning is associated with age of identification. For instance, Shattuck et al. (2009) analyzed data from 13 sites participating in the Centers for Disease Control and Prevention's 2002 multisite ongoing autism surveillance program. They used data from health and education records to examine factors that influence the timing of community-based identification and diagnosis. Several factors were associated with a younger age of identification, including being male and having an IQ of 70 or lower.

A second point is that level of functioning impacts the psychometric properties of the different instruments used to identify and diagnose people with ASD (e.g., Gotham et al. 2009; Hus et al. 2013; Norris and Lecavalier 2010). Generally speaking, diagnostic accuracy is better in school-age children with mild-to-moderate ID. Diagnostic criteria and rating instruments are not as accurate in toddlers, preschoolers, adolescents, or in individuals with more severe ID or no ID. The take-home message here is that level of functioning impacts who is identified, when in life they are identified, and diagnostic complexity/certainty.

Finally, level of functioning impacts the classification of ASD. For a diagnostic system to be meaningful, individuals in one category should be similar to one another on key variables such as clinical features, psychological profiles, history, and course, but different from people in other categories (Cantwell 1996; Robins and Guze 1970). In other words, a good classification scheme minimizes within-group variability and maximizes between-group variability. Diagnostic groups cannot be valid if they are not reliable. Taken as a whole, the literature on *DSM-IV*-defined ASD subtypes suggested blurry lines between categories. In fact, one could argue that the reliability problems were largely related to level of functioning. In their review of 22 studies comparing ASD subtypes, Witwer and Lecavalier (2008) concluded that the differences observed across ASD subtypes might be better explained by IQ than diagnostic subtypes. For example, many of the differences across ASD subtypes in terms of core diagnostic features, executive functioning, motor functioning, or behavior problems were equally explained by IQ differences (i.e., differences across groups disappeared when analyses controlled for IQ). The model of ASD in the *DSM-IV* did not provide enough diagnostic clarity on how to distinguish ASD subtypes, especially for higher-functioning children. The subsequent study by Lord et al. (2012) further elaborated on this phenomenon. They examined 2102 children with ASD across 12 university-based autism centers. Although the distribution of children's behaviors on standardized measures was similar across sites, the distributions of clinical best-estimate diagnoses were dramatically different. In other words, even when using the same diagnostic instruments and standardized procedures across sites, there was regional variability in which ASD subtype was given to a child. Clinicians used non-ASD specific behavioral characteristics such as hyperactivity, age, and IQ to assign ASD subtypes. For example, some sites gave children with higher IQs a diagnosis of Asperger's syndrome, while other sites used PDD-NOS.

The inability to establish the reliability and validity of ASD subtypes in *DSM-IV* was an impetus for a new definition of ASD. In contrast to *DSM-IV, DSM-5* identifies a smaller number of more general symptoms in social communication. These symptoms are expected to be present in *all* individuals with ASD regardless of age and developmental level, but symptoms can be manifested in many different ways. Clinicians will now specify the presence of ID, making it an explicit consideration in the ASD diagnosis. The new edition of the *DSM* shows promise, but its validity, particularly its incremental validity over predecessors, will only be determined with time.

Core Diagnostic Features

Correlational and cross-sectional analyses of IQ and ASD symptoms have found evidence for negative correlations between level of functioning and a number of ASD symptoms. Lower verbal IQ and lower nonverbal IQ have been associated with more ASD symptoms (Gotham et al. 2009; Spiker et al. 2002). In fact, Spiker et al. (2002) found that ASD symptoms and nonverbal IQ represented parallel dimensions of severity such that children with lower nonverbal IQ also tended to have the most severe ASD symptoms, particularly in the social-communicative domain. Another example is the study by Ben Itzchak et al. (2008), which grouped 44 preschoolers with autism by cognitive level to form three groups: Normal (IQ > 90), Borderline (70 < IQ < 89), and Impaired (50 < IQ < 69). They compared the groups' scores on the *Autism Diagnostic Observation Schedule* (Lord et al. 2000). Compared to the two other groups, the Impaired group had significantly higher scores in the reciprocal social interaction domain. The Impaired group also had higher scores than the Borderline group in the stereotyped behavior domain. Differences were not found between the Borderline and Normal groups.

In recent years, more attention has been paid to the relationship between IQ and restrictive repetitive behaviors and interests (RRBI). Several studies have proposed two main groups of RRBI (Bishop et al. 2013; Bishop et al. 2006; Cuccaro et al. 2003; Szatmari et al. 2006). One group consists of repetitive sensory and motor behaviors (RSMB) such as hand/finger manneriisms, unusual sensory interests, repetitive use of objects/parts of objects, and rocking. The other group of RRBI, often referred to as "insistence on sameness" (IS), consists of behaviors related to rigidity or resistance to change which include difficulties with changes in routine, resistance to trivial changes in environment, and compulsions/rituals.

The two broad groups of RRBI seem to have different relationships with level of functioning. Whereas RSMB have been found to be negatively related to age and IQ in some people, IS behaviors have shown either no relationship or positive relationships with level of functioning. Most of the studies examining the relationship between level of functioning and different types of RRBI have been conducted with some combination of the 12 items found on the *Autism Diagnostic Interview—Revised* (ADI-R; Rutter et al. 2003). Of course, this fairly small pool of items limits the associations that can be found. For instance, in most studies, self-injurious behaviors (SIB) and circumscribed interests (CI) were not included. In one of these studies, in a sample of 830 children who ranged from 15 months to 11 years of age, Bishop et al. (2006) found a significant interaction between nonverbal IQ and chronological age, such that nonverbal IQ was more strongly related to the prevalence of several RRBI in older children. The prevalence of a number of repetitive behaviors (e.g. repetitive use of objects, hand and finger mannerisms) was negatively associated with nonverbal IQ. However, the prevalence of certain behaviors (e.g. circumscribed interests) was positively associated with nonverbal IQ. In a sample of 339 individuals with ASD, Szatmari et al. (2006) reported RSMB to be negatively correlated with adaptive skills, while IS was positively correlated with autistic symptoms in the communication and language domain. In addition, analyses suggested moderate familial aggregation among affected sibling pairs within the IS but not the RSMB factor, suggesting that IS may be under familial/genetic control, while RSMB appears to simply reflect variation in developmental level. Lam et al. (2008) reported three factors in their sample of 316 people with autism: RSMB, IS, and CI. They also reported that RSMB were associated with a variety of subject characteristics such as IQ, age, social/communication impairments, and the presence of regression or skill loss. IS was associated with social and communication impairments, whereas CI appeared to be independent of subject characteristics. Based on sib-pair correlations, they also reported that IS and CI (but not RSMB) appear to be familial. Finally, one recent study replicated these findings using both the ADI-R and the *Repetitive Behavior Scale—Revised* (Bodfish et al. 2000) in a large independent

sample (Bishop et al. 2013) recruited from the Simons Simplex Collection, a North American multisite university-based research study that includes families with only one child with an ASD.

Adaptive Behavior

A number of large-scale studies on adaptive behavior have been published in the past 10 years or so. Evidence suggests that as children with ASD become older, their adaptive skills are more impaired relative to age-matched peers (Kanne et al. 2011; Szatmari et al. 2003). This implies that individuals are failing to acquire skills commensurate with their chronological and cognitive growth. The "typical autism profile" is described as one marked by the most substantial delays in socialization, lesser delays in adaptive communication, and relative strengths in daily living skills (Bolte and Poustka 2002). Even this "typical" adaptive behavior profile is impacted by the level of cognitive ability. The profile has been documented in higher-functioning ASD samples (e.g., Klin et al. 2007; Perry et al. 2009; Saulnier and Klin 2007). Yet, in lower-functioning individuals, adaptive behavior has been found to be commensurate or higher than mental age in some cases (e.g., Fenton et al. 2003; Perry et al. 2009). In other words, the "autism profile" is less likely to manifest as the gap increases between chronological and mental age. Kanne et al. (2011) reported on this relationship using the *Vineland Adaptive Behavior Scales-II* (Sparrow et al. 2005) in a large sample of verbal youth with ASD. Specifically, children with an IQ < 70 (n = 223; average IQ = 54) had an average adaptive behavior composite score of 66, whereas the children with an IQ > 70 (n = 855; average IQ = 98) had an average adaptive behavior composite score of 79.

Behavior and Psychiatric Problems

As used here, the term "behavior problems" describes those challenging and impairing behaviors often seen in people with ASD such as self injury, tantrums, aggression, and property destruction. Behavior problems are contrasted with the psychiatric disorders defined in the DSM. The relationship between behavior and psychiatric problems is not well understood. There is little doubt that they co-occur but there is no evidence to suggest a systematic relationship between the two. Rather, the evidence seems to suggest that behavior problems are nonspecific indicators of distress and dysfunction (Witwer and Lecavalier 2010).

It is well-documented that children with ASD present with high rates of behavior problems (Brereton et al. 2006; Lecavalier 2006). As previously discussed, ID has been commonly associated with more severe ASD (Fombonne 2009). In addition, behaviors challenging to caregivers such as aggression have also been associated with ASD severity (Jang et al. 2010). A few studies have specifically reported on the relationship between level of functioning and behavior problems. In a sample of 487 young people with ASD between the ages of 3 and 21 years, Lecavalier (2006) reported that children with more impaired adaptive skills had significantly more problems on most of the prosocial and problem behavior subscales of the *Nisonger Child Behavior Rating Form* (Aman et al. 1996). Estes et al. (2007) reported on the relation between level of functioning and behavior problems in a sample of 74 6–9-year-olds. Participants were classified as lower and higher functioning using nonverbal IQ, verbal IQ, and communication scores on the *Vineland Adaptive Behavior Scales* at age 6 years. Likewise, problem behaviors were assessed with a variety of rating scales. Results suggested that higher-functioning children at age 6 years displayed increased internalizing symptoms by age 9 years, whereas lower-functioning children displayed higher hyperactivity, attention problems, and irritability by the age of 9 years. These data suggest that level of intellectual functioning may be a risk factor for different patterns of associated symptoms by later childhood. The trend of greater behavior problems in lower-functioning individuals is also true for adolescents and adults with ASD. In their longitudinal study, Shattuck et al. (2007) found that individuals with comorbid ID had more behavior problems than those

without ID. Furthermore, behavior problems in individuals with comorbid ID improved less over a period of 4.5 years as compared to those without ID.

SIB and aggression are two of the most vexing behavior problems. There are actually few large-scale studies examining the relationship between level of functioning and these two behavior problems in ASD. This is rather surprising given their clinical importance and the amount of resources allocated to them. One exception is the recent study by Duerden et al. (2012) who investigated the relationship between SIB and intellectual functioning in a sample of 250 children with an average chronological age of 88 months. Children with lower IQ were more likely to engage in SIB. IQ explained a small portion of the variance in the SIB data, but not as much as IS (i.e., IS was more predictive of SIB than IQ). This association between low cognitive functioning and high rates of SIB in children with autism is consistent with some prior findings but at odds with studies suggesting that IS is either not correlated or positively correlated with IQ (e.g., Bishop et al. 2006; Szatmari et al. 2006). The exact reason for higher rates of SIB in lower-functioning individuals is a mystery although several explanations have been proposed, including impaired memory systems that lead to an inability to learn about pain. From research among individuals with ID without ASD, we have known for decades that SIB tends to increase with severity of functional handicap (Schroeder et al. 2001).

Dominick et al. (2007) conducted one of the few studies examining factors associated with aggression in 67 children with ASD. They found that the presence of aggression was associated with lower IQ, poorer expressive and receptive language, and RRBI. In a much larger sample, Kanne and Mazurek (2011) did not find an association between aggression and level of intellectual or adaptive functioning, language ability, or ASD severity. This was a large (n = 1380) and well-characterized sample taken from the Simons Simplex Collection. Of note, however, is the fact that only four items from the ADI-R (current and ever ratings of *aggression towards caregivers or family members* and *aggression towards non-caregivers or nonfamily members*) were used to measure aggression.

Similar to behavior problems, high rates have also been reported for psychiatric problems (Gadow et al. 2005; Simonoff et al. 2008). Commonly reported psychiatric symptoms include attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders, and anxiety and fears. Conceptualization of these syndromes in ASD is a matter of debate. On the one hand, it is possible that psychiatric disorders are independent of ASD and reflect co-occurring conditions. On the other hand, it is possible that they are inherently associated with core features of ASD and are distributed from low to high in children with ASD, similar to language and intellectual skills. It could also be that psychiatric symptoms and ASD are separate but not independent, in that the presence of one amplifies the other because of certain genetic and environmental influences. There are currently not enough data to declare a winner in the debate, but there are some studies that lend support to the *DSM-IV* as a valid conceptualization of psychiatric disorders in children with ASD. For instance, Lecavalier et al. (2009) submitted parent and teacher ratings of *DSM*-based symptoms to confirmatory factor analysis. The sample in this study consisted of 498 children aged between 6 and 12 years. The authors found support for ADHD, oppositional defiant disorder (ODD), conduct disorder, generalized anxiety disorder (GAD), and mood/dysthymic disorder as diagnostic categories in ASD. In fact, they reported similar indices of fit for children with ASD and a comparison group of typically developing children. If the DSM was not a valid conceptualization for these children, symptoms would not correlate with one another in this organized fashion. Interestingly, fit indices improved when analyses were only conducted on children with an IQ > 70, which could suggest that the DSM conceptualization becomes less valid as IQ declines. Along the same lines, Gadow and colleagues provided additional support for the validity of psychiatric disorders in ASD by examining patterns of comorbidity and genetic and psychosocial risk factors (Gadow et al. 2008a, 2008b, 2008c; Gadow et al. 2006; Gadow et al. 2012).

The differential patterns of comorbidity and risk factors observed in ASD were similar to those observed in typically developing children. One thing is clear, whether these problems are part of ASD or independent from them, they are impairing, fairly common, and appropriate targets for psychosocial or pharmacological treatment (Kaat et al. 2013).

A few studies have examined the relationship between level of functioning and psychiatric problems using structured psychiatric interviews. Witwer and Lecavalier (2010) used the parent version of the *Children's Interview for Psychiatric Symptoms* (P-ChIPS), a structured interview based on the *DSM-IV,* to compare psychiatric symptom endorsement rates of children with ASD. They found that children with an IQ < 70 had fewer reported symptoms than those with an IQ ≥ 70. Lower-functioning individuals were more likely to be subsyndromal (defined as having symptoms for a disorder and related impairments, but falling short of full diagnostic criteria by one or two symptoms) for GAD and nonverbal individuals were more likely to be subsyndromal for ODD. Symptom endorsement also varied based on language levels. Contrasting results were reported in the only epidemiological sample examining risk factors for psychiatric disorders in children with ASD (Simonoff et al. 2008). In this sample of 112 10–14-year-olds, neither IQ nor adaptive behavior scores were associated with increased rates of psychiatric disorders. The authors explained the lack of association between IQ and psychiatric disorders as possibly indicating that ASD trumps other risk factors, whereby the influence of IQ is diminished in this population due to the more potent risk factor of ASD itself.

Anxiety in ASD has been the object of several recent published reports (Hallett et al. 2013; van Steensel et al. 2011; White et al. 2009). Unlike externalized behavior problems, it may be difficult to infer which behaviors are driven by anxiety and which are due to ASD in the absence of direct verbal expression from the individual. In addition to expressive verbal ability, the problem of attribution is likely to be influenced by IQ. Gotham et al. (2013) reported on the relationship between anxiety and IS in a sample of 1429 individuals, also recruited from the Simons Simplex Collection. These constructs were minimally associated with each other and with chronological age and verbal IQ. Neither anxiety nor IS was associated with other core autism diagnostic scores. Anxiety was associated with a variety of other psychiatric and behavioral symptoms, including irritability, attention problems, and aggression, while IS was not. These data showed that anxiety and IS appear to function as distinct constructs, each with a wide range of expression in children with ASD across age and IQ levels.

Hallett et al. (2013) examined parent-reported anxiety symptoms in a sample of 415 children with ASD who participated in one of four multisite psychopharmacological trials. They used 20 items measuring anxiety from the *Child and Adolescent Symptom Inventory* (CASI-Anxiety; Gadow and Sprafkin 1997, 2002; Sukhodolsky et al. 2008). Items measuring panic, post-traumatic stress symptoms, and obsessions are not included on the CASI-Anxiety. They observed that high scores on the CASI-Anxiety were associated with being verbal, having an IQ of 70 or above, and showing higher levels of inappropriate speech, irritability, and hyperactivity. They also observed that children in the upper quartile on the CASI-Anxiety had higher Vineland scores, which is consistent with previous findings showing positive associations between IQ and anxiety in ASD (Weisbrot et al. 2005; Witwer and Lecavalier 2010). Interestingly, considering the individual items of the CASI-Anxiety, the most- and least-endorsed statements were the same in the high- and low-functioning groups. Items such as "*acts restless or edgy,*" "*has difficulty falling asleep,*" and "*is extremely tense and unable to relax*" are directly observable and were most commonly endorsed by parents. The high language requirements for items starting with "worries" or "complains" apparently limited the rate of endorsement in the lower IQ group, which in turn contributed to the lower CASI-Anxiety mean score. Nonetheless, youth with IQ of 70 or greater had significantly higher mean scores than the ID group on the 10 scale items with low verbal demand. This suggests that, even when

considering the more observable aspects of anxiety, higher-functioning children exhibited more anxiety than children with lower IQ.

In contrast to these findings, the meta-analysis by van Steensel et al. (2011) found higher rates of anxiety disorders in children with lower levels of intellectual functioning (defined by the cross-study median split IQ of 87), suggesting that children with lower IQ do experience anxiety and exhibit anxiety-driven behaviors even if the anxiety is not expressed verbally. In the Hallett et al. (2013) study, children with the highest levels of anxiety also had more behavior problems than those who were less anxious. This could reflect the overall behavioral disturbance of the children in this sample, albeit this relationship has been reported elsewhere (Gotham et al. 2013). These associations could also suggest that anxiety may amplify other behavioral problems or that a combination of higher IQ coupled with more severe behavior problems poses a greater risk for anxiety difficulties. This is particularly interesting as irritability and hyperactivity have been associated with lower IQ (e.g., Estes et al. 2007). Clearly, more research on the correlates of anxiety is needed.

Outcome

Level of functioning has been shown to impact the natural course of ASD and response to treatment. The long-term course of ASD is generally understood to involve lifelong impairments with a modest trend toward improvement (Seltzer et al. 2004). However, individual characteristics such as severity of cognitive deficits influence the trajectory of the disorder and its eventual outcome. The most frequently cited characteristics that influence the course of ASD are ID and overall language ability. The absence of ID and the presence of better language skills in early childhood have been consistently associated with a greater likelihood of improvement over time in children and better adult outcomes (Baghdadli et al. 2007; Howlin et al. 2004; Shattuck et al. 2007; Szatmari et al. 2003).

In their seminal follow-up study of 68 adults who met criteria for ASD as children and had a nonverbal IQ above 50, Howlin et al. (2004) found that individuals with a childhood nonverbal IQ of 70 or higher had a significantly better outcome in adulthood. Outcome was quite variable and, on an individual level, neither verbal nor nonverbal IQ proved to be consistent prognostic indicators. Howlin and colleagues found that social and adaptive outcomes were more highly correlated with verbal IQ than with nonverbal IQ. They concluded that having an IQ over 70 is necessary but not sufficient for an optimal outcome. In their sample of 241 adolescents and adults with ASD, Shattuck et al. (2007) examined change in autism symptoms over a 4.5-year period. Although the majority of the sample showed improvement, those individuals with comorbid ID improved less over time. In fact, the absence of ID was the most robust predictor of change in symptoms.

The term "optimal outcome" has been used to describe children who once met criteria for ASD but now present without significant symptoms of ASD and function in the average range of intelligence (Fein et al. 2013). Helt et al. (2008) reviewed long-term outcome studies and concluded that between 3 and 25% of individuals with ASD eventually lost their diagnosis, although very few of the studies reporting these outcomes explicitly addressed the question of whether their social and communication abilities were fully typical. They also concluded that early predictors of better outcomes included higher IQ, receptive language, imitation, motor skills, earlier diagnosis and treatment, and a diagnosis of PDD-NOS rather than autistic disorder. A recent study by Fein et al. (2013) confirmed that optimal outcome is more likely in individuals with higher cognitive functioning and somewhat milder initial symptoms.

Studies of early interventions in children with ASD have also found IQ, age at treatment initiation, and early language skills to be among the strongest predictors of response to treatment. These findings have been reported among a variety of intervention types (e.g., Ozonoff and Cathcart 1998), but mainly for early intensive

behavioral intervention (Howlin et al. 2009). In spite of the convergence across studies in terms of identified predictors of successful response to treatment, it is important to note that there is great variability at the individual level and there have been few sufficiently powered studies to allow adequate testing of moderators of treatment response. Nonetheless, studies with different research designs have reached similar conclusions. For instance, Sallows and Graupner (2005) examined the predictors of best response to a 4-year applied behavioral analysis-based treatment for 24 children with ASD. Treatment outcome was best predicted by pretreatment imitation, language, and social responsiveness. Children with higher pretreatment IQs were more likely eventually to have IQs in the average range (75% of children with IQs between 55 and 64 vs. 17% of children with IQs between 35 and 44). Similarly, a study of 44 preschool children who received 2 years of early intensive behavioral intervention indicated that the best outcomes were achieved by those who had higher IQs and adaptive skills at baseline (Remington et al. 2007). Finally, Ben Itzchak and Zachor (2007) examined predictors of outcome of early behavioral intervention in preschool children with autism who underwent 1 year of intensive behavioral interventions at 35 h per week. Children with ID demonstrated slower acquisition of receptive and expressive language skills, play skills, and nonverbal communication skills after 1 year of treatment. In this study, progress in the receptive language domain was highly related to pretreatment cognitive and social abilities. Children with higher pretreatment cognitive ability or with better social reciprocal abilities made more gains in their receptive language.

Unfortunately, there are few long-term follow-up studies of children with ASD who attended intensive intervention programs in their preschool years. Magiati et al. (2011) reported on 36 children with ASD (mean age of 3.4 years) enrolled in relatively intense, specialist preschool programs (minimum of 15 h of intervention per week for 2 years). They assessed the children 2 years (mean age 5.5 years) and 7 years (mean age 10.3 years) posttreatment on cognitive skills, language, adaptive behavior, and severity of ASD symptoms. Baseline IQ and language and adaptive behavior skills were predictive of outcome 7 years posttreatment. This study highlighted that while overall group improvements may be evident, the rate and nature of these improvements is highly variable across individual children. Further investigation of the specific child characteristics that affect treatment effectiveness is required as level of functioning alone does not explain the variability in response rates.

Current evidence on the role of IQ for positive outcomes in early intervention might be the most compelling we have. One reason for this is that many of the recent psychosocial treatment studies such as social skills training or cognitive behavior therapy for anxiety have focused on high-functioning individuals (Kaat and Lecavalier 2014; Lang et al. 2010). The story is quite different when it comes to the use of psychotropic medicines, which may very well be the most commonly used type of treatment for people with ASD (Lecavalier and Gadow 2008). Overall, multiple surveys show that approximately half of people with ASD take psychotropic medicines and that older age and lower level of functioning are associated with increased patterns of use (Rosenberg et al. 2010; Witwer and Lecavalier 2005). Of course, factors external to clinical presentation likely affect odds of psychotropic medication use. For instance, in the Rosenberg et al. (2010) study, people residing in a poorer county or in the south or midwest regions of the USA had increased rates of psychotropic medication use. Beyond the actual use of medicines, the key question is whether or not children with high- and low-functioning ASD respond differently to the same agents. Much like the early intervention studies, there are few sufficiently powered controlled trials that allow the study of moderation (Siegel and Beaulieu 2012). Some of the largest studies that have been conducted in the field to date have not found an effect of level of functioning on clinical response (Arnold et al. 2010; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network 2005; King et al. 2009). On some levels this is surprising as there is evidence that IQ impacts response rates

for some medicines in non-ASD populations. For instance, Aman et al. (2003) reported that children with low IQ and ADHD clearly respond to methylphenidate, but their rate of beneficial response appears to be well under that of average-IQ children and more varied.

Conclusions

ASD represents a heterogeneous group of neurodevelopmental disorders that overlap with ID. Differences in intellectual ability help to explain some of the vast heterogeneity associated with ASD. The past decade has taught us that the etiology of ASD is complex, but there is a relationship with level of functioning. High- and low-functioning individuals with ASD have different profiles in terms of core and associated clinical features. Lower-functioning individuals tend to have more social-communicative deficits and RSMB. There is great diversity across individuals, but the natural course of ASD and response to treatment seems to be impacted by level of functioning. Several studies have shown higher levels of functioning to be significantly associated with better clinical outcomes. Ultimately, it is hoped that identifying more phenotypically homogenous subgroups will facilitate efforts to understand the causes and treatment of ASD.

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