Autism and autism spectrum disorders: diagnostic issues for the coming decade

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A decade and a half have elapsed since DSM-IV and ICD-10 appeared. During this time the convergent definitions of autism and related disorders in these two diagnostic systems have stimulated tremendous research. In this brief review we summarize areas of progress and continuing controversy, including approaches to diagnosis in more cognitively able individuals on the autism spectrum, diagnosis in very young infants, the issue of subtypes, and the potential contribution of genetic research. The use of dimensional assessments has some advantages as do the insights from prospective studies. At this point it will be important to study not only causative factors but developmental processes disrupted in these disorders. Keywords: Autism, diagnosis, PDD.

The 65 years following Kanner’s description of the syndrome of infantile autism (Kanner, 1943) witnessed many advances in the diagnosis and classification of autism and related conditions; these included the recognition of autism as a disorder, i.e., apart from childhood schizophrenia, an increasingly well elaborated set of diagnostic guidelines, and a growing recognition of the ‘broader spectrum’ of conditions apparently related to autism but which probably outnumber it five fold (Fombonne, 2005). Understandably, if somewhat paradoxically, the vast majority of research studies have focused on the core diagnostic concept – autism.

The current approach to the diagnosis of autism, as exemplified in DSM-IV (APA, 1994) and ICD-10 (WHO, 1994), has worked reasonably well in terms of facilitating both research and clinical service; it has stimulated more sophisticated diagnostic and screening approaches (Lord & Corsello, 2005). These gains have been reflected in the dramatic increase in research on autism and related conditions (Volkmar, Lord, Bailey, Schultz, & Klin, 2004) and an increased awareness on the part of the public and media (Fombonne, 2005). As expected, this increase in research has also raised important questions about syndrome boundaries in this heterogeneous group of conditions. This includes the conditions currently ‘officially’ recognized (Asperger’s disorder, Rett’s disorder, Childhood disintegrative disorder) and the ‘subthreshold’ category either termed (in DSM-IV) Pervasive Developmental Disorder Not Otherwise specified (PDD-NOS) or (in ICD-10) atypical autism. Much less research has been conducted on the ‘broader spectrum’, although there has been much speculation about whether subgroups/subtypes exist and how they might best be conceptualized (Towbin, 2005). Other tensions surround the issue of diagnosis as a ‘ticket’ for services – a problem referred to as diagnostic substitution (Fombonne, 2005). It is also commonly, but incorrectly, assumed that approaches to subtyping should be universally applicable, e.g., that classification for educational services eligibility must be the same as for etiological research. The ICD-10 addressed this issue, in part, by creating ‘clinical’ and ‘research’ criteria separately, while the DSM system utilizes one set of criteria for both uses.

In this paper we review current issues in diagnostic nosology and potential future directions. Of necessity this review must be highly selective in nature and we limit ourselves to a handful of topics including methodological considerations as well as to areas of current debate: subtyping the ‘broader spectrum’ of autism, the distinction between Asperger’s disorder and high-functioning autism, and understanding the importance of developmental deterioration. For purposes of presentation we take the current official DSM/ICD categories as a starting point for discussion but emphasize that ultimately any number of other approaches may be more useful.

Methodological considerations

In some sense, considerations of subtyping relevant to clinical management are relatively straightforward. In contrast to the research context where, as much as possible, heterogeneity is avoided, clinical work is based on developing individualized profiles of strength and weakness in terms of social-communicative disabilities and cognitive and communicative abilities (NRC, 2001). Although the issue of co-morbidity in autism (and all developmental disorders) is a particularly challenging one, the individualization of psychopharmacological treatments is critical even when co-morbid conditions are
present (Scahill & Martin, 2005). Various factors in the future may, however, change this situation, e.g., if PDD subtypes could be more strongly related to treatments or if specific etiologies or pathophysiological mechanisms can be used to guide treatment.

At present, however, the issue of treatment building upon an individual’s profile of strengths or weaknesses is more important than distinctions between autism, PDD-NOS or Asperger’s syndrome; indeed, levels of cognitive functioning and communicative speech remain probably the most robust predictors of outcome (Howlin, 2005), although work on children who do NOT respond to treatment remains an important priority (NRC, 2001).

Another important consideration has been the ability to move beyond simple categorical approaches and define new measures of social or communicative ability/disability. At present there is a tendency to assume that the move from categories of autism to Asperger’s syndrome or to PDD-NOS reflects some aspect of decreasing severity, but this is not a particularly satisfactory approach. A different approach might use some summary score on an instrument like the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999) for addressing issues of metrification and correlation between symptom domains, although it is clear that the ADOS was not designed to represent a scale of affectedness (Lord & Corsello, 2005) but a novel approach to better achieve reliable categorical classification. This is a general problem reflecting difficulties in instrument and item development in autism and related disorders, e.g., a verbal child might receive a higher score than a nonverbal child because there are more potential items to sample. Recent attempts using other approaches (e.g., Gotham, Risi, Pickles, & Lord, 2007), may produce more useful indices of severity.

Normative, dimensional assessment instruments have also proven useful in autism. For example, the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) was used in a series of studies to document, against a normative sample, communicative and socialization delays in individuals with autism and related disorders, e.g., a verbal child might receive a higher score than a nonverbal child because there are more potential items to sample. Recent attempts using other approaches (e.g., Gotham, Risi, Pickles, & Lord, 2007), may produce more useful indices of severity.

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A somewhat different approach has been employed in the Social Responsiveness Scale (SRS; Constantino & Todd, 2003). The SRS was developed to provide an instrument to quantify social skills in genetic studies of large samples of twins (Constantino & Todd, 2003). Although sampling various behaviors, its uniqueness lies in its normative approach to a measure of sociability applicable to the entire population. Thus it can be used as a dimensional instrument for studies of larger and broader samples not simply limited to categorically diagnosed groups. For example, it has been used to capture ‘subclinical’ traits in family members – an issue particularly relevant to the issue of broader autism phenotypes (Constantino et al., 2004; Constantino & Todd, 2005; Bailey, Palferman, Heavey, & Le Couteur, 1998; Le Couteur et al., 1996), or as a means to evaluate the contribution of specific genetic variants to social traits in the general population (Duvall et al., 2007).

The use of dimensional approaches builds on a long history (in the use of tests of intelligence and language) which may provide better approaches to subtyping. Thus the addition of explicit dimensions of functioning (along cognitive or communicative ability) might be particularly helpful in addition to categorical diagnosis.

Attempts to subtype might also be based on specific brain mechanisms or neuropsychological constructs. These approaches build on a long history of study of potential mechanisms which has, in recent years, become increasingly interesting as specific processes of interest have been identified. Although the data are limited to date, categorical diagnostic categories have seemed less important than specific neuropsychological constructs (Schultz, Romanski, & Tsatsanis, 2000). For example, the observation of macrocephaly in young children with ASD (Courschene et al., 2001) is of considerable interest for future studies.

Advances in genetics have raised the important questions for future research in subtyping. It is well accepted that the combination of genetic heterogeneity and diagnostic uncertainty complicates efforts to identify autism genes (Gupta & State 2007). Consequently, it has been taken as axiomatic that the ability to define phenotypic subgroups reflecting more homogenous biological mechanisms will be crucial to successful efforts at illuminating autism risk alleles. In fact, recent progress in genetic research both supports and challenges this basic notion.

On the one hand, early success in mapping genes leading to defined syndromes within the PDD spectrum, most notably the identification of the role of MECP2 in Rett syndrome (Amir et al., 1999), demonstrated that tightly-defined phenotypes could be leveraged to identify causative ASD genes. More recently, a growing number of studies have supported the utility of using so-called endophenotypes in gene discovery efforts. These are observable phenomena that exist along the continuum from a genetic variant or variants to a clinical syndrome, including specific neuroanatomic or neuropsychological processes, combinations of symptom clusters, patterns of clinical expression, levels of language ability, and so forth (Dawson et al., 2002;
DiCicco-Bloom et al., 2006). For instance, the use of language endophenotypes has improved statistical support for the involvement of certain regions of the genome and genes in ASD (Wassink, Brzustowicz, Bartlett, & Szatmari, 2004; Alarcon, Cantor, Liu, Gilliam, & Geschwind, 2002; Alarcon et al., 2008), though such efforts have not yet led to the identification of an unambiguous autism risk locus.

Conversely, several lines of evidence suggest that the strategy of relying on cross-sectional phenotyping of any sort to enhance biological homogeneity within the autism spectrum may have important limitations. First, in the few cases in which genetic mutations have been identified in patients with idiopathic or non-syndromic autism, it is clear that identical lesions expressed throughout development may result in a very broad range of clinical findings, i.e., a single mutation in the germ line may increase the risk for autism, mental retardation without social disability, Asperger’s syndrome or PDD-NOS (Jamain et al., 2003; Laumonnier et al., 2004). In fact very recent findings have associated the same single genetic anomaly with increased risk for autism or schizophrenia and a host of other psychiatric diagnoses (Weiss et al., 2008). Moreover, recent successful efforts at gene discovery in other complex disorders have provided strong evidence that the key to successful initial efforts at autism gene discovery will be recruiting a sufficiently large number of clinically-identified patients (O’Roak & State, 2008).

At the present time, it is not yet clear which approaches will prove to be most fruitful. Given the available evidence, it seems likely that if endophenotyping proves to be instrumental to gene discovery it will need to extend beyond cross-sectional evaluation and categorical approaches as exemplified in DSM and ICD (Volkmar & Klin, 2005). One of the recurrent problems with the study of endophenotypes, given the early onset of autism, is the complex interaction of genetic and non-genetic factors throughout development; it will be important that attempts to subtype include careful consideration of developmental trajectories in the attempt to disentangle specific effects.

Subtyping issues, higher-functioning autism and the broader ‘autism spectrum’

Typically when the ‘autism spectrum’ is used it refers to three of the currently recognized categorical groups: autistic disorder (strictly defined), Asperger’s disorder (AS) and PDD-NOS. As we noted previously, the majority of individuals (probably five fold) fall into the PDD-NOS category. For autism, strictly defined, there is a rich body of work on the diagnostic concept and excellent agreement on the clinical diagnosis of autism (Klin, Lang, Cicchetti, & Volkmar, 2000). As we shall discuss shortly, the situation with AS is more complex but the situation vis-à-vis PDD-NOS is even more complicated. As a diagnostic concept PDD-NOS has its own origins, in part of the work of Rank (1949) and in the ‘atypical’ concept first used in DSM-III to refer to ‘subthreshold conditions’. ICD-10 differentiates various subtypes of what it terms atypical autism, DSM-IV only one. The original DSM-IV approach to the category allowed it to be used when any single feature of autism was present; this approach was clearly unfortunate (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999). Accordingly in DSM-IV TR an attempt was made to make the concept more stringent by requiring at least some social feature and either a communicate or unusual behavior feature as well. As noted by Towbin (2005), various attempts have been made, with limited success, to differentiate subgroups within the broader PDD-NOS group, e.g., cases which have, in addition, significant attentional difficulties (Sturm, Fernell, & Gillberg, 2004). To date, no consensus has emerged and the limited available data poses basic obstacles for future research. This is particularly unfortunate given the common (but not necessarily correct) tendency to equate autism with autism spectrum disorder (ASD).

Another complexity arises since the term ASD is often applied more globally to individuals with cognitive ability in the normative range. This often leads to misuse of the term ASD to stand for ‘high-functioning’ autism when, in fact, on the one hand, more able individuals with autism have always been recognized, and the frequency of ‘autistic-like’ symptoms (especially stereotyped mannerisms) increases with decreasing IQ. Thus there tends to be a confound among what are technically several different categories – autism without mental retardation (sometimes termed higher-functioning autism (HFA)), Asperger’s syndrome (AS) and PDD-NOS. The question of how best to approach these cases has been widely debated (Klin, Saulnier, Tsatsanis, & Volkmar, 2005b; Miller & Ozonoff, 2000) and a consensus has not emerged. Unfortunately, while there are some data relevant to these issues, this work has been limited in many respects, e.g., inconsistent definitions, small sample sizes, circular reasoning (Klin et al., 2005b).

Several aspects of Asperger’s original (1944) report suggest areas of overlap (social disability/autism) and difference from autism, e.g., preserved language ability, high rate of similar difficulty in family members, unusual fact-based special interests. Prior to inclusion of the condition in DSM-IV and ICD-10 studies on the topic had been limited; data from the DSM-IV field trial (Volkmar et al., 1994) provided some support for inclusion of AS, although ambivalence about its inclusion as a ‘new’ category was expressed in the final definition adopted, which has proven problematic in several respects (Klin, McPartland, & Volkmar, 2005a; Miller & Ozonoff, 1997). As a result, at least three rather different definitions have emerged which yield, not surprisingly,
rather different results (Klin et al., 2005a). To simply designate ‘high-functioning autism’ as Asperger’s adds relatively little; what would be of much greater interest would be whether there is some evidence for the utility of AS as a diagnosis based on differences in implications for treatment, mechanisms of disorder, etc. (see Cantwell, 1996). This question must presently be regarded as unsettled, although the fundamental notion of Asperger’s (1944) that social difficulty was combined with preserved language (verbal) ability raises the intriguing potential that both of AS representing a different pathway into social disability and for differences in treatment than would be more typical in autism. The observation of different patterns of neuropsychological functioning in AS as compared to HFA would also be quite relevant. Ultimately this will best be clarified by adoption of more stringent definitions of the condition (where differences from autism would presumably be most readily observed) or explicit declination of the various approaches to diagnosis, e.g., Asperger’s types I, II, or III. There is some danger that inconsistencies in diagnostic approach will lead to premature foreclosure of this discussion. It is likely that these various issues will be clarified with the availability of longitudinal samples followed prospectively from early childhood. Such studies, however, are only beginning to appear (Lord et al., 2006).

Subtyping issues for the ‘disintegrative’ disorders

Two of the disorders presently recognized within the PDD class are characterized by regression – childhood disintegrative disorder and Rett’s disorder. Both are relatively rare and are often not seen as being typical of or subsumed under the ASD label. The inclusion of Rett’s in DSM IV/ICD-10 was much debated (Gillberg, 1994; Rutter, 1994). At the time the argument for inclusion had not to do with its being some version of autism (which longitudinal data had clearly indicated was not the case) but that it be included somewhere, and, given the potential in early life for the condition to be confused with autism, it seemed most sensible to include it within the PDD category. Of course, since that time there has been an explosion of interest given the discovery of the X-linked MECP2 gene mutation in at least 80% of affected girls (Amir et al., 1999). As with Fragile X syndrome, it remains unclear whether any behavioral commonalities with autism reflect shared neurobiological mechanisms (Dykens & Hodapp, 2001) but the ability to understand how a single gene defect manifests itself has been particularly exciting since it allows for development of animal models, studies of brain mechanisms, and so forth. In some ways the study of the rare syndrome of CDD may have much more relevance to autism since it resembles autism in most respects but its onset is, by definition, only after some time (typically years) of normal development. Although CDD is quite rare, the patterns of onset and clinical presentation are highly distinctive (Volkmar, Koenig, & State, 2005) and the outcome appears even worse than that in autism with children typically making little improvement following their regressive episode. The agreement can be made, although without much data in support, that many such cases may be related to the expression of some central nervous system malady; usually, however, extensive medical evaluation fails to reveal such associations and rather than continuing to deteriorate, in most cases of CDD the child’s behavior and development stabilize at some low level but do not then further deteriorate.

As a diagnostic entity CDD is of interest for several reasons over and above the obvious and tragic clinical implications the condition has for children and families. In the first place the disorder is so distinctive that it would seem ripe for delineation of specific genetic or other mechanism. Given the small number of cases seen, comparatively speaking, collaborative research would be needed to assemble a sufficient number of cases for study. A second, and perhaps just as interesting, reason for study of this rare condition is its potential for overlap with the relatively common finding of developmental regression in autism.

By definition CDD is diagnosed in DSM-IV and ICD-10 only when development has been normal up to age 2 years with a marked regression after that point. If defined in this way CDD is clearly uncommon. However, a large group (20–25%) of parents of children with classic autism (which develops before age 3) report that their child has had a regression (Lord, Schulman, & DiLavore, 2004). Unfortunately, the data on the nature of regression in autism and its prognostic significance itself remains a topic of much debate (Luyster et al., 2005; Werner & Dawson, 2005). Part of the difficulty here may arise from different approaches to definition, i.e., careful study of parent report of regression suggests that this may be less common than would first appear, with many parents reporting regression in children who either were already delayed or whose pattern was less one of regression than one of a developmental plateau (Siperstein & Volkmar, 2004). Prospective studies (of large groups of infants) may help clarify these issues. A focus on children with clear-cut regression may be scientifically productive.

Diagnostic and subtyping issues in infants

Given that Kanner first thought that autism was a congenital disorder it is somewhat surprising that only now are we seriously studying infants at risk for autism (Zwaigenbaum et al., 2007). Follow-up studies of 2-year-olds referred for possible autism...
has suggested three rather different patterns, with some children exhibiting all required features by age 2, others exhibiting some (particularly the social-communicative ones) but not others (the restricted interests) until around age 3, and a small number of infants who appear to have autism before 3 but don’t after age 3 (Lord, 1995). Although a chronological age of 3 and a mental age of about 18 months appear to have emerged as diagnostic watersheds (after which diagnosis is easier), this view has also been questioned by some reports (Charman et al. 2005), suggesting continued potential for symptom change over time. As a practical matter, one of the limitations in this area has been the need to rely either on parent report or on parent-supplied videotapes; one problem for diagnosis has been the limitations of categorical criteria for very young children (Coonrod & Stone, 2005). Research has shown some promising areas for investigation of specific developmental markers and potential physiologic ones as well (Chawarska, Klin, & Volkmar, 2008). The relatively recent advent of prospective studies offers considerable promise in helping elucidate diagnostic issues as we disentangle some of the earliest features and processes of autism apart from their subsequent impact on development. The potential for major advances in this area is great and may have important implications for clarification of subtyping issues.

Summary

Traditional approaches to classification have focused on the extent to which subtypes help us predict course, response to treatment and outcome (Szatmari, 2000) or to other relevant issues such as family history, differential implications for treatment, and so forth (Cantwell, 1996). It should be noted that in the nearly 15 years since the current official approaches were adopted the quality and quantity of research on autism and related conditions have increased dramatically. However, much of this work has centered on more ‘classical’ autism. In this paper we have, briefly, outlined some areas which appear fruitful for advancing research in this area. Clearly the use of consistent, clear criteria is greatly to be desired but in some respects uniformity may be even less important than careful specification of the focus of study. The use of newly developed alternative, dimensional assessments may help disentangle much of the current confusion about ASDs broadly defined and their relationship to more strictly diagnosed autism. The ability to provide better sample specification, e.g., through additional ratings of levels of communicative or cognitive ability, would greatly add to the diagnostic system. Prospective studies offer great potential, as do new approaches focused on specific developmental processes. The current diagnostic approach leans heavily on both current examination and past history (particularly around issues of onset) and prospective research may help clarify how relevant these distinctions truly are. In considering various alternatives for DSM-V and ICD-11 it will be important to seriously evaluate currently available research and highlight those issues most likely to advance research and clinical enterprises. To this end the ‘residual’ nature of PDD-NOS remains a source of frustration for parents, clinicians, and researchers alike. Research on this group of cases is critical if we are to avoid perpetuating our continuing ignorance of it. As has been pointed out elsewhere (Klin, Jones, Schultz, & Volkmar, 2003), it is important to study not only causative factors but developmental processes disrupted. And indeed the apparent variations in ‘onset’ may have more to do with the specifics of the timing of the disruption of basic socialization processes.

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Key points

- Current approaches, categorical and dimensional, to diagnosis of autism and related conditions have facilitated considerable research and, in turn, generated area of current research focus and controversy.
- Areas of controversy include diagnostic distinctions among more cognitively able individuals, diagnosis of autism in infants, and alternative approaches to subtyping.
- The focus on the broader spectrum of disabilities associated with autism has expanded the boundaries of the condition and raised important questions for family genetic and molecular genetic studies.
- The identification of potential endophenotypes will facilitate research but faces some challenges given the early onset of autism and the complex interaction of genetic and nongenetic factors in subsequent development.

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References


