Seeing the Forest AND the Trees

Disentangling Autism Phenotypes in the Age of DSM-5

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Abstract

to be added!

Throughout his distinguished career Ed Zigler was concerned with many important issues in Developmental Psychopathology: Early Child Developmental and Head Start, Learning and Cognitive processes, Social Policy, and developmental disabilities – particularly intellectual deficiency or what used to be termed mental retardation. Sometimes these issues overlapped as Ed and his many students examined aspects of learning as well as cognitive and behavioral phenotypes of specific forms of intellectual disability (e.g., (Burack et al., 1997; Glick et al., 1987; Glick & Zigler, 1986; Weisz & Zigler, 1979, Robinson et al., 2000). As time has gone on these issues have assumed increasing importance with the growing sophistication of genetic methods to identify very specific genetic etiologies and potential pathways of developmental disorders (Dykens et al., 2000; Hodapp & Dykens, 2007, 2012). Attention has also focused on specific similarities and differences in cognitive processing (Burack & Volkmar, 1992; Volkmar et al., 1990) and in more general attempts to develop conceptual models of conditions like autism/Autism Spectrum Disorder (ASD, Jackson & F.R., 2019; Vivanti et al., 2019). These issues have taken on considerable importance in autism as the genetics of the condition as the complexities of genetic contributions have begun to be distinguished (Yuenn et al., 2019).

The recognition of Infantile Autism

Leo Kanner was the first person to clearly delineate the syndrome of “early infantile autism” (Kanner, 1943) which he identified as an inborn disturbance of affective contact defined by two key features: 1) marked lack of social engagement from very early in life and 2) insistence on sameness and avoidance of change. This description essentially defined one very specific and indeed the classic phenotype of autism.

Although 'new' to the developing field of developmental psychopathology there is little doubt that cases had been seen (without being recognized) much earlier, e.g., in some of the training schools here in the U.S. in the 1800's (Donvan & Zuker 2016) and likely even in the much earlier reports of 'feral or 'wild' children – most likely children with autism or severe neglect who had either been abandoned by their parents or who had run away from them (see (Boswell, 1989, Candland, 1995, Favazza, 1977, Anderson et al., 2012). Many aspects of Kanner's description remain quite applicable today but it is clear that some early speculations about autism were fundamentally wrong. Among the false leads for early research was the initial confusion of autism with childhood schizophrenia, Kanner's observation of very high levels of occupation and academic success in parents (this leading both to an assumption that parents might be involved in syndrome pathogenesis and autism was not seen in the 'lower' social class', and that autism was not associated with other medical conditions. Most notable given what he saw as the lack of dysmorphic features of these children and their ability to engage in some nonverbal tasks at very high levels Kanner's early impression that infantile autism was not associated with intellectual disability (or as it was then termed mental retardation). This misimpression was corrected as follow-up studies became available and the first wave of children identified functioned, as adults, mostly in the severely impaired range with only a relative handful (Kanner, 1971, Eisenberg & Kanner, 1956, Howlin et al., 2014). Other early assumptions, i.e., that autism was a disorder associated with higher social status, was an early form of childhood schizophrenia, and was not associated with other medical conditions also proved false over time (Jackson & F.R., 2019). For many years research was limited particularly by the confusion of

autism with childhood onset schizophrenia. However, very quickly it did become apparent that despite very low levels of overall adaptive and cognitive functioning, some individuals, perhaps 10%, had some special skills or ability usually involving some aspects of memory like drawing, musical ability, calendar calculation, and so forth. (Hermelin, 2001, Selfe, 1979, Wiltshire, 1988). Indeed shortly after Kanner's initial publication Kurt Golstein and colleagues (Scheerer et al., 1945) a case of an 11-year-old boy with an IQ of 50 who had remarkably able for number manipulation, verbal memory, and calendar calculation classified as an idiot savant, was studied over a period of 5 years by means of standard tests, special experiments, and a reliable record of his previous development. His special skills were in music, verbal retention, number manipulation, and calendar calculations but who otherwise was severely impaired in his daily life and cognitive ability. Their term for this condition ("idiot savant", Rimland & Fein, 1988; Treffert, 1988) has now effectively been changed to autistic savant as such cases are almost invariably associated with autism and intellectual disability. The observations of these islets of amazing preserved ability (in the face of otherwise severe cognitive dysfunction) immediately raised important questions about continuities and discontinuities with other types of intellectual deficiency and the question of the course of cognitive development in these cases.

Research on autism gradually began to accumulate as it became clear that autism was not associated with schizophrenia (Rutter, 1972), was seen in all social classes (Wing, 1980), was highly genetic (Folstein & Rutter, 1977), and related to evidence of central nervous system dysfunction like seizures (Volkmar & Nelson, 1990). It also became clear that the early psychodynamic treatments for autism were not

effective but structured teaching could be effective (Bartak & Rutter, 1973) and evidence based treatment approaches began to be developed at academic centers in the U.S. (National Research, 2001). These treatments models began to increase in breadth and sophistication essentially with a focus on helping the developing child compensate for his/her lack of social connectedness (National Research, 2001).

Attempts were made to more carefully define the syndrome of infantile autism (Rimland, 1964, NSAC, 1978; Rutter, 1978) and by 1980 infantile autism was first recognized as an official diagnostic category in DSM-III (Association, 1980). This definition was, in many ways, very much in line with Kanner's original description emphasizing the earliest form of the disorder both in the title it gave "infantile autism" and the criteria it provided. The issue of potential developmental change was addressed by having another category for 'residual infantile autism' for cases that had once met criteria for the infantile form of the condition but no longer did so. Given the need for a new 'class' or category for the disorder autism and associated conditions were placed in a new class of conditions – the Pervasive Developmental Disorders (PDD). Criteria were also given for childhood onset forms of the disorder (i.e., after some years of early normal development) and for a subthreshold category atypical PDD for cases not meeting full criteria but with problems suggestive of autism. (Cohen et al., 1986)

DSM-III Infantile Autism – What is In and What was Out

At the point in 1980 when autism was first officially recognized several points are of note. In the first place it appeared that autism was one of the best examples of a "disorder" in child psychiatry, i.e., in that it did not seem to shade off into normalcy.

(Garmezy & Rutter, 1983). Furthermore autism, as then strictly defined, was relatively rare impacting perhaps one in several thousand children and was much more common (three to five times) in boys than in girls (Fombonne, 1997). In addition at that point in time most cases (over 50%) of cases were mute as adults and functioned in the intellectually deficient range although unusual patterns of cognitive abilities were frequently observed (Volkmar & Cohen, 1986). Many of these notions began to change as research on the condition increased following its official recognition in DSM-III (1980). This included the marked growth in research on genetic and neurobiology (Rutter, 2013). Greater awareness also led to diagnosis and the potential for implementation of evidence based intervention (Reichow & Volkmar, 2011). In turn this appeared to lead to better outcomes in many cases with some children making remarkable gains either in the preschool years or sometimes in adolescence (Fein et al., 2013). Diagnostic tests (interviews and in person assessments) began to be developed (Lord et al., 2014) partly in the hope that consensus on the diagnostic concept could stimulate genetic research that identified underlying genes (Rutter et al., 2014). All these factors set the stage for a developing and now ongoing debate on the boundaries of autism and the autistic phenotype.

The Expanding Diagnostic Concept and Broader Autism Spectrum

Perhaps somewhat paradoxically the agreement on the classic 'Kannerian' view of autism in DSM-III (APA, 1980) touched off a much larger debate about the boundaries of autism. These issues included a debate about the potential validity of other conditions, notably Asperger's, and 'atypical' cases – the beginning of the broader

autism phenotype debate as well as related discussion of the need for a more developmentally appropriate definition of autism (as compared to the one in DSM-III and the growing and expanding awareness of the complexities of genetic factors.

The debate about the broader autism phenotype is, in many ways, a long standing one. Both before and after Kanner cases were reported that have some similarity to those he reported. for example, Rank (Putnam & Rank, 1953; Rank, 1949, 1955) proposed a concept she termed atypical personality development – a term that became remarkably similar to the term atypical pervasive developmental disorder in DSM-III (APA, 1980). More important the year after Kanner's initial. report Hans Asperger (Asperger, 1944) description a series of boys who had marked social troubles but preserved language abilities along with notable special history's and often a positive history of social difficulties in family members. His same use of the word autism immediately suggested an important point of similarity although throughout his life, even after becoming familiar with Kanner's description, he regarded the two conditions as distinctive (Asperger, 1979). The disorder attracted little attention until Wing's review of the topic (Wing, 1981) a year after DSM-III appeared. Subsequent to that time research interest gradually increased although so did best approaches to diagnosis of the condition with some advocating strict adherence to Asperger's original ca reports, other attempt to modify Wing' s description so that several difference conceptualizations occurs although all see it as having some similarity to autism (see (Klin et al., 2000; Szatmari, 1991). Essentially three rather different views of Asperger's as a concept .

Additionally work on the group of cases with many features of autism but not meeting full DSM-III criteria began to increase (Towbin, 1997, Towbin, 2014). This work began, in important respects, to converge with a growing body of work in genetics (Rutter, 2014; Thapar & Rutter, 2008; Yuenn et al., 2019) showing the complexities of genetic contributions to autism and the potential for many forms of autism (Gillberg et al., 2019). As the term autism spectrum disorder came into common use and began to replace the term pervasive developmental disorders (Lord, 1997) there began to be recognition of a broader autistic phenotype (BAP) suggesting that like many other conditions autism did not simply shade off into normalcy. (Ingersoll et al., 2014; Piven et al., 1997) questioning the early notion that autism did NOT shade into normalcy but was associated with a range of problems

From DSM-III- to DSM-5

Although DSM-III helped stimulate an explosion of research on autism as soon as DSM-III appeared problems with it were apparent. These included a lack of developmental awareness and an overfocus on 'infantile' autism, imitations of the provided monothetic criteria, rational for other disorders included in the PDD category (e.g., residual infantile autism and childhood onset PDD, Wing & Gould, 1979, Wing, 1989a, 1989b, Volkmar, 1987). Attempts were made to address some of these problem in DSM-III-R (Association, 1987) although this version was quickly replaced by a new version DSM-IV(Association, 1994). The definition for autistic disorder (as it was now termed) was developed in collaboration with that for ICD-10 (Organization, 1994) and based on a large multi-site, international field trial (Volkmar et al., 1994). This definition included 12 criteria groups into the traditional three area of problems in

social interaction, communication and play, and restricted and repetitive behaviors and interests apparent from early in life. In this new approach over 200) combinations of criteria could lead to an autism diagnosis. It appeared to cover the range of ages and intellectual functioning well and converged well with expert clinician diagnosis. In addition both DSM-IV and ICD-10 included a number of other 'new' conditions including Asperger's disorder, a category for the very rare cases of autism that developed after a period of normal development, and a subthreshold category of atypical autism/Pervasive Developmental Disorder not otherwise specified.

The recognition and definition of Asperger's disorder was the focus of considerable debate (Ghaziuddin, 2011; Mayes et al., 2001; Woodbury-Smith et al., 2005). Depending on the diagnostic approach used potentially important differences were, however, found from autism relative to family history and neuropsychological profiles (Woodbury-Smith et al., 2005, Klin et al., 1995). The DSM-IV system worked well for nearly two decades and stimulated a massive body of work on autism as well as on conditions like Asperger's and the broader autism phenotype.

The entire DSM was revised for a 5th edition appearing in 2013. The new DSM-5 (Association, 2013) differed from its predecessor many ways. Some important, positive changes were made relative some changes in categories and their definitions both these were not without controversy (Greenberg, 2013). A new term autism spectrum disorder was adopted both for the condition itself and the category to which it belonged. It was observed, probably not surprisingly, that approaches to the diagnosis of Asperger's and PDD-NOS varied considerably from site to site so these terms were dropped in favor of the overall diagnostic term (Lord et al., 2012, Happe, 2011). The

new approach to diagnosis for autism spectrum disorder grouped social communication into a single criterion set all of which had to be met and a second set of four restricted interest receive interests/repetitive behavior criteria two of which had to be met. The latter also included for the first time an item on hypo-hypersensitive as a definition feature of the condition (that latter had not worked well in the DSM-IV field trial (Volkmar et al., 1994). The initial report of the DSM-5 approach (Huerta et al., 2012) suggested that it had a good balance of sensitivity and specificity. A new communication disorder category (social communication disorder- SCD) was now include din DSM-5 for individuals with problems in pragmatic communication who did not have the difficulties with restricted interest observed in ASD.

Unfortunately a number of issues were immediately apparent. As a practical matter this new approach vastly reduced the number of criterion combinations that could lead to an autism spectrum disorder diagnosis (over 2000 in DSM-IV and 12 in DSM-5) /Secondly the actual term for the class of conditions - autism spectrum disorder – while welcome in many was in the singular, i.e., it failed to recognize the reality of the broader autism phenotype (Ingersoll et al., 2014). The first study of a draft DSM-5 criteria set provided worrisome results (Matson et al., 2012) and subsequently a reanalysis of cases from the DSM-IV field trial but using the final new DSM-5 criteria set confirmed and expanded these. concern (McPartland et al., 2012). in the McPartland et al. study many individuals with clinician assigned diagnosis's of autism who function above the intellectually deficient range lost their diagnosis and the vast majority of those with Asperger's and PDD-NOS also did so. Concerns were also quickly raised about exclusion of toddlers from early intervention because of the stringency of the new

approach (Barton et al., 2013; Matson et al., 2012). A number of studies have now confirmed these findings (see (Smith et al., 2015) for a meta-analysis). These concerns result in a last-minute change in DSM-5 that 'grandfathered in' cases who previously held 'well established' diagnoses of conditions like Asperger's and Pdd-NOS and autistic disorder. This solution did not, of course, help individuals just attaining diagnosis and has had a particular impact in the U.S. where diagnostic label is often closely associated with intervention services. In summary although presenting some advances the newer DSM-5 definition, despite the name change, has reverted to a narrower view of the diagnostic concept. This narrower DSM-5 approach has related to classification of major social disability into special groups like women, very young children, cultural diverse group, and the broader autism spectrum in general. This is particularly unfortunate since the growing body of research indicates that with identification and treatment many children can make important gains and no longer suffer the associated problems of intellectual deficiency once so common in autism (Magiati & Howlin, 2019)

Current Controversies and Complexities

Since DSM-5 appeared (2013) a number of controversies have continued or emerged. In the first place the problem of Asperger's disorder remains unresolved. There is general agreement that the DSM-IV definition could have been substantially improved and that authors essentially adopted their own forms of it making it unsurprising that different centers used the term in different ways (Woodbury-Smith, 2005 #28287). In the meantime the number of studies on Asperger's dramatically increased and new data were emerging just as the decision was made to drop the

category. For example Chiang and colleagues conducted a large meta-analysis of autism and Asperger's and found different neuropsychological profiles associated with the two conditions (Chiang et al., 2014). Similarly Sharma et al. (Sharma et al., 2012) reviewed nearly 70 research studies using various approaches to diagnosis of AS and noted areas of overlap with autism as well as some important potential differences. Other studies (de Giambattista et al., 2019, Montgomery et al., 2016) also have supported recognition of Asperger's in some form as an official category. At the moment the category is in somewhat of a state of limbo with cases diagnosed before DSM-5 retaining their label while new cases are no longer identified (but continue of course to exist). Best approaches to including Asperger's clearly are an important topics for the next iteration of DSM-5.

Other issues arose with the dropping to the subthreshold PDD-NOS concept and including a new social communication disorder (SCD) partly in its place. The large majority of cases of PDD-NOS as DSM-IV diagnosed no longer meet criteria for autistic disorder in DSM5 but continue to merit service provision and support. It is not simply the case that these cases automatically 'make' the new SCD label given that cases with restricted repetitive behaviors are excluded from that diagnosis (see (Ozonoff & Miller, 2014; Tufan, 2014) for contrasting views). The entire rationale for this concept has indeed been questioned (Flusberg, 2018). Effectively this very large group of cases no longer has a diagnostic 'home' in the DSM even as their frequency is increasingly realized and likely accounts for at least some of the apparent dramatic increase in cases of autism in epidemiological surveys (Meyers et al., 2019).

Developmental Issues

The first reports of autism were of school age children and this group, particularly boys of borderline and mild intellectual disability, have traditionally been the general target group of diagnostic specific instruments (Lord et al., 2014). The challenges for diagnostic criteria is, of course, to address the entire age range of the condition. For autism has been a challenge, at times, both for adults, and infants and young children. Given that autism is clearly an early onset disorder the latter problem might seem somewhat paradoxical

Autism in Infants and Young Children

As noted previously DSM05 presents some challenges for diagnosis in younger children particularly those who are more cognitively able. As for all individuals Both the social-communication problems of autism AND the restricted behavior features must be present. Just as in older children and adults there is a wide range of heterogeneity but even when antedated by parental concern the more obvious behavioral manifestations of ASD emerge for most children in the second year of life and often are initially expressed in the realm of social-communicative features rather than restricted behaviors, i.e., lowered levels of social communication, limited social attention, lack of social engagement and eye contact (Chawarska, Klin, Paul, et al., 2009; Chawarska et al., 2014; Miller et al., 2017). Delays in these areas can also be noted in other conditions like intellectual deficiency and language disorders making use of appropriate comparison groups critical in evaluating best approaches to diagnosis (Macari et al., 2020; Manwaring et al., 2018).

Studies using high risk groups, e.g., infant siblings, also show that some siblings will have early difficulties suggestive of ASD but may then go on to develop more typically or to become part of the broader autism phenotype (BAP) (Macari et al., 2012) .

Studies of this group of high-risk siblings have helped to clarify the earliest features of ASD. By 12 months those who later go on to have a diagnoses of autism are usually showing atypical social-communicative responsivity (see Chawarska et al., 2020). The restricted interests/repetitive behavior domain behaviors begin to appear at the same time early in life but also are seen in typically developing infants where they do not, however, consistently engage in attention with an adult social partner (Chawarska et al., 2020). (Chawarska et al., 2014). Unfortunately these generalizations don't always apply in the individual case (Elison et al., 2014;

As noted previously the approach adopted in DSM-5 is rather less flexible than in DSM-IV (Mandy et al., 2012). As a result the youngest children who go on to have ASD may not yet meet criteria for the condition. In one sample of 1-3 year olds 72% of those diagnosed who would have had a PDD diagnosed in DSM-IV did not meet ASD criteria using DSM-5 (Mayes, Black, & Tierney, 2013). In general the loss of the more flexible polythetic and 3 domain approach in DSM-IV seems to have had a major impact for this group of cases (Barton et al., 2013).

Another set of issues arise for adolescents and adults for whom the question of an Autism Spectrum diagnosis arises for the first time. This issue has become more frequent with the awareness of the broader autism phenotype and an awareness that individuals with milder autism traits may not be diagnosed until adulthood (Lai & Baron-Cohen, 2015). Often these are very cognitively able individuals who may present with

complex mental health histories. As we have noted elsewhere (Volkmar et al., In Press) several issues arise. How well do current criteria apply in this group? Do unusual diagnostic assessments instruments assist with diagnosis? What are the needs of this group of cases?

Adults who present with a question of a possible ASD diagnosis are a diverse group and present several challenges (Lai & Baron-Chen, 2015; Huang et al., 2020). Sometimes symptoms are milder and only come to attention in new situations, e.g., as in going to college. Sometimes this can be because learning demands change, and students need support although in at least one study by White and colleagues between .7 and 1.9% of a large freshmen sample met criteria for ASD but had not previously been diagnosed. At other time a high enough functioning adult will be able to make it with supports but when these disappear or radically change the extent and severity of needs become apparent. As we discuss shortly a number of these cases are women where it is possible a milder phenotype delays diagnosis till later in life. Adults seen in mental health services, and some will already have other diagnoses.

In these adults coming to diagnosis later there may be different patterns of syndrome expression, e.g., where special interests and routines have some advantages for occupational success. On the other hand many adult mental health providers are much less likely to recognize the underlying social disability so that miss-diagnosis and inappropriate treatment may be more common (see (Volkmar et al., In Press) .

Application of the more child-centered DSM-5 criteria may be problematic (Magiati and Howlin 2019). It does appear that some of the standard assessment instruments may not work as well in adults as in children while others may work reasonably well (Fusar-

Poli et al., 2017). Several adult focused assessments are now available to address this problem. {Volkmar, In Press #33149}. Sadly, appropriate supports and services are often lacking (Huang et al., 2020).

Gender

As noted above issues of gender, specifically the nature of the ASD phenotype in females, have been the focus on increasing debate. For many years the apparent preponderance of boys with autism meant that much less attention was focused on girls with some studies excluding girls from their sample to try avoiding technical complexities like gender matching. As noted above both the early diagnostic criteria and assessment were developed with a focus on boys of school age with mild to borderline levels of intellectual disability. As a result of these factors important aspects of the female phenotype has been overlooked. As we discuss elsewhere {Volkmar, In Press #33149} there has been an implicit assumption that diagnostic criteria are gender neutral. The available literature on this topic suggests that, females with ASD must have great degrees of impairment and symptomatology (Dworzynski et al., 2012); this is of interest in that females, in general, tend to present with more internalizing symptoms profiles as compared to males (Mandy et al., 2012). It has also been suggested that compared to males females are more likely to be able to engage in 'camouflaging' or 'pretending to be normal' also accounting for later presentation and diagnosis . (Bargiela et al., 2016). Several authors have now questioned the long standing assumption of male predominance in ASD, (Becker 2012, Constantino and Charman 2012, Haney 2016).

Over the last decades several theories have been proposed to account of what appears to be male predominance of ASD. One theory is that females must present with great symptoms. (Volkmar, Szatmari, & Sparrow, 1993). Others have speculated that there may be a protective effect of being female = protective effect (Robinson, Lichtenstein, Anckarsäter, Happé, & Ronald, 2013). It does generally appear to be the case that females as a group exhibit some noteworthy phenotypic differences from males. For example, they exhibit lower levels of the restrictive receptive behaviors (Charman et al. 2017; Frazier et al. 2013), less severe sensory issues and better joint attention (Oien, Hart et al. 2017) and a lesser degree of social avoidance (Oien, Vambheim et al. 2018). These differences in phenotypic expression could then result in less pronounced ASD symptoms and failure to meet usual diagnostic criteria or be below symptom threshold on usual assessment instruments. Is it noteworthy that in large scale study of screening instruments sex differences are observed very early in life (Oien, 2017 #28724) .

Cultural Issues

In recent years increased interest in ASD research and treatment has increased dramatically in the developing countries. (Freeth, 2014 #26633) As interest has increased so have issues of cultural similarities and differences in the expression, assessment, and treatment of autism and related conditions. While the body of work on this topic is relatively small that clearly are some areas of potential difference, e.g., regulation of eye contact across cultures (Freeth, Milne et al. 2014) that might impact usual Western oriented assessments. As Freeth and colleagues rightly note clearly the bulk of research has been conducted within the well-developed Western cultures and

Japan. Often screening and diagnostic instruments have been translated but sometimes with mixed results in non-Western (Freeth et al., 2014).

Even within the U.S. the study of ethnic minority groups has suggested some potential complexities in application of usual models/instruments in the diagnosis of autism. In one study of Hispanic children issues arose with application of usual research diagnostic instruments particularly around the area of communication resulting in lower sensitivity and specificity (Vanegas et al. 2016). Similar issues have been noted by others studying minority groups within the U.S. , e.g.. , Tek & Landa (2012 (Palmer, Walker et al. 2010; Mandell, Ittenbach et al. 2006).

Screening instrument results may vary in different minority groups, e.g., (Khowaja et al., 2015).

(Dai et al., 2020). (Kimple et al., 2014; Rea et al., 2019; Windham et al., 2014).

Differences have been noted more generally in the application of DSM5 in different developed countries, e.g., this system seemed to work well in the U.K. but not so in Finland (Mandy, Charman et al. 2014). One of the great complexities of research in this area is the broader meaning and context of studies of how autism may be viewed differently across cultures (Grinker, Kang-Yi et al. 2015).

Summary to be added

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