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AUTISM SPECTRUM (C DISSANAYAKE, SECTION EDITOR)

Autism Spectrum Disorder: Defining Dimensions and Subgroups

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Abstract Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder associated with the presence of social-communication deficits and restricted and repetitive behaviors. In the latest conceptualization of ASD, these two behavioral dimensions represent the core defining features of ASD, whereas associated dimensions, such as intellectual and language ability, provide a means for describing the ASD heterogeneity. In addition, the characterization of ASD subgroups, defined by the presence of known medical, genetic, or other psychiatric disorders, furthers our understanding of ASD heterogeneity. This paper reviews the history of autism, describes its core defining features, and provides an overview of the clinically and etiologically relevant subgroups that add to the complexity of this condition.

Keywords Autism · Autism spectrum disorder · DSM-5 · ICD-11 · ADHD · Anxiety · Depression · Disruptive behavior · Catatonia · Kanner · Asperger · Pervasive developmental disorder · Dimension · Subtype · Specifier

Introduction

Consideration of autism as a spectrum disorder can be traced back to the careful and detailed clinical observations by Kanner and Asperger, who described children with a broad range of atypical behaviors and intellectual abilities [1, 2]. Understanding and describing this heterogeneity in autism spectrum disorder (ASD) is critical to the work of both clinicians and researchers, and to achieving a full understanding of individuals with this diagnosis. Recent research, particularly in the biological sciences, has brought attention to the limitations of the categorical approach to defining ASD, and promotes the use of dimensional assessments to examine the core and associated features of ASD, an approach adopted in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3, 4]. Despite this new focus on dimensional assessment, the identification of subgroups, based on the presence of co-occurring psychiatric, medical, and/or genetic risk conditions, continues to be of importance to research and clinical practice. This review provides an overview of the history of autism diagnosis (Table 1) and describes both the dimensional and categorical approaches to characterizing ASD as outlined in the new DSM-5 (Fig. 1).

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Identification and Classification of Autism

The earliest publications on autism described the atypical quality of social interactions between child and adult, documented the presence of repetitive object use and insistence on sameness, and distinguished between the categorical diagnoses of autism and childhood-onset schizophrenia. In the influential article entitled "Autistic disturbances of affective contact," Dr. Leo Kanner published a series of case studies describing eight boys and three girls between the ages of 2 and 11 years who were exhibiting a similar cluster of symptoms [1]. He described the children's preference for using objects repetitively in lieu of socially interacting with others and wrote, "the outstanding, 'pathognomonic' fundamental disorder is the children's *inability to relate themselves* in the ordinary way to people and situations from the beginning of life." He noted numerous commonalities across these children, including an atypical "relation to people," language consisting mainly of naming objects, literalness, delayed echolalia, excellent rote memory, repeating phrases with personal pronouns in the exact way heard, early concern about

Table 1 Diagnostic labels for autism spectrum disorder: a comparison of DSM and ICD diagnoses and subtypes

DSM Diagnoses and subtypes	Edition	ICD Diagnoses and subtypes	Edition
Schizophrenia Childhood type	DSM-II, 1968[1]	Schizophrenia Infantile autism	ICD-8, 1967[2]
Pervasive developmental disorder Infantile autism Childhood onset pervasive developmental disorders	DSM-III, 1980	Psychoses with origin specific to childhood Infantile autism Disintegrative psychosis Other Unspecified	ICD-9, 1977[3]
Pervasive developmental disorder Autistic disorder Pervasive developmental disorder-not otherwise specified	DSM-III-R, 1987	Psychoses with origin specific to childhood Infantile autism Disintegrative psychosis Other Unspecified	ICD-9, 1977[3]
Pervasive developmental disorder Autistic disorder Asperger's disorder Pervasive developmental disorder-not otherwise specified	DSM-IV, 1994	Pervasive developmental disorders Childhood autism Asperger's syndrome Atypical autism Other pervasive developmental disorders Pervasive developmental disorder, unspecified	ICD-10, 1993[4]
Childhood disintegrative disorder Rett's disorder		Other childhood disintegrative disorder Rett's syndrome Overactive disorder with mental retardation and stereotyped movements	
Autism spectrum disorder	DSM-5, 2013	Autism spectrum disorder (proposed)	ICD-10, Beta draft, 2013[5]

Notes: 1. Described by Rapoport 2009, 2. Described by Leekman et al., 2002, 3. Information obtained online at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD-9/ucod.txt, 4. Information obtained online at http://www.who.int/classifications/icd/en/GRNBOOK.pdf, 5. Information obtained online at http://apps.who.int/classifications/icd11/browse/f/en

hearing impairment, strong reactions to noises and moving objects, "monotonous repetition" of noises, motions, and verbal utterances, and "limitations in the variety of spontaneous activity." Furthermore, and critical to psychiatric practice at the time of writing, Dr. Kanner distinguished between childhood schizophrenia and the cluster of autism symptoms he had observed. Similarly, in 1944, Dr. Hans Asperger provided descriptions of a case series of children, primarily boys, emphasizing the presence of social impairments and withdrawal, eccentric behavior, emotional impairments, ritualized and stereotyped behavior, learning and attentional problems, as well as giftedness, and suggested that these symptoms represented a personality disorder which merged into the 'normal' continuum [2, 5].

The observations by Drs. Kanner and Asperger remain relevant today and have shaped the current definition of autism. Despite these well-documented case studies, which were published in the early 1940's, the American Psychiatric Association (APA) and the World Health Organization (WHO) did not immediately recognize autism as a distinct diagnostic category. As shown in Table 1, in 1967, the International Classification of Diseases, Eighth Revision (ICD-8) mentioned autism for the first time, listing "infantile autism" under the schizophrenia grouping, whereas the APA Diagnostic and Statistical Manual of Mental Disorders, Second Edition (DSM-II), published around the same time, specified "schizophrenia, childhood type" without any reference to autism [6, 7]. In 1977, the ICD-9 specified "infantile autism," "disintegrative psychosis," "other," and "unspecified" under the grouping "psychoses with origin specific to childhood" [7]. Thereafter, the DSM-III subtypes "infantile autism" and "childhood onset pervasive developmental disorders" were incorporated under the diagnostic category of "pervasive developmental disorder" [8]. Additions to the DSM-III-R included similar subtype entries with slightly modified wording, "autistic disorder" and "pervasive developmental disorder – not otherwise specified (PDD-NOS)," but changes were not made to the ICD [9]. By the early 1990's, the DSM-IV saw the addition of three subtypes: "Asperger's disorder," "childhood disintegrative disorder," and "Rett's disorder," which mirrored the most recent modifications to the ICD-10 [10, 11].

In the newly published DSM-5, the overarching term, "pervasive developmental disorder" is replaced by "autism spectrum disorder," which is the designation also proposed for the ICD-11 [4, 12]. This term represents the idea that the core features of ASD can be measured dimensionally and that they fall along a continuum of severity [13, 14]. No diagnostic subtypes (e.g., Asperger's disorder and PDD-NOS) are listed;

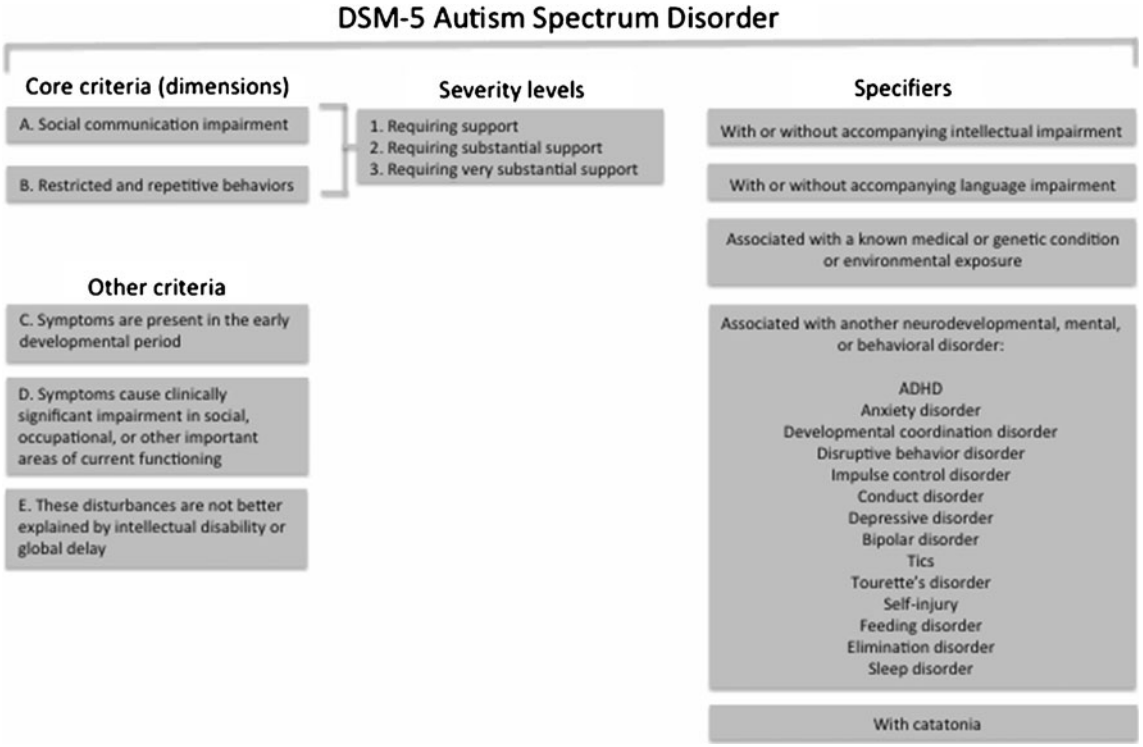

Fig. 1 DSM-5 ASD diagnostic criteria and specifiers

instead, specifiers are provided to indicate the presence of intellectual and/or language impairment as well as the severity level of the core ASD symptoms. Further, any known genetic or medical disorders are recorded and other co-occurring neurodevelopmental, mental, or behavioral disorders are indicated [4].

Preliminary research studies comparing the DSM-IV and DSM-5 classifications have demonstrated that most individuals diagnosed with DSM-IV autistic disorder, Asperger's disorder, or PDD-NOS also meet DSM-5 criteria for autism spectrum disorder; however, some studies have found that the DSM-V criteria poorly identified higher-functioning individuals [14–16]. These mixed results suggest that further research is required to determine if modifications to the new criteria will be needed in subsequent revisions of the DSM-5.

Objective Measurement of Autism Symptoms

In the 1960's and 1970's, researchers sought to develop objective measures of the core ASD symptoms, resulting in the development of rating scales used to aid in the identification of ASD [17]. One of the primary measures to emerge included the Childhood Autism Rating Scales (CARS), which assessed 15 autism-related symptoms based on observation and/or caregiver report. In addition, the CARS yielded an overall ASD severity score and a cutoff score used to determine the presence or absence of autism [18]. Additional assessments were developed to standardize the methods for assessing parent- and teacher-reported symptoms and clinical observation and to determine the presence of an ASD as well as the severity of ASD symptoms [19–22]. Although the first instruments focused on the assessment of children, ASD assessments have progressively focused on measuring symptoms across the lifespan, including infancy and adulthood [23–25]. Researchers have also turned their attention toward examining the distribution of ASD-related traits in the population as a whole [26] and using ASD assessments to examine the broader autism phenotype [27–30].

The view that core ASD symptoms fall along a continuum or spectrum existed prior to the DSM-IV [7]. Current research supports this view and suggests that Asperger's syndrome and PDD-NOS overlap with "high-functioning autism," that these subgroups are not identified reliably across clinicians, and that the outcomes for PDD-NOS and autism are indistinguishable [7, 31, 32]. In addition, longitudinal studies have shown that PDD-NOS represents a mixed diagnostic group, is not a stable diagnosis, and often represents individuals with social-communication deficits in the absence of repetitive behaviors or activities [33, 34]. Further examination of subgroups comes from studies seeking to identify empirically defined subgroups. Factor analysis of core ASD symptoms commonly yields one, two, or three factors that represent social deficits, communication deficits, and/or the presence of repetitive

behaviors [35–38]. For the DSM-5, two core factors or dimensions are stipulated, one representing impairment in reciprocal social communication and social interaction, and the other representing restricted, repetitive patterns of behaviors, interests, or activities [4]. Factor analysis and cluster analysis techniques also reveal the importance of emotional and behavioral regulation or other regulatory processes (e.g., sleep and feeding) in describing the heterogeneity of ASD [39–41]. Consideration of such factors supports the identification of subgroups with varying symptom profiles but does not provide precise empirical support for the DSM-IV and earlier subgroup classifications [37, 42].

Subtyping ASD According to Cognitive and Language Abilities

In the DSM-5, in addition to the evaluating two core ASD domains, the characterization of ASD involves specifying whether or not intellectual and language impairments are present. A majority of individuals with ASD have mild to moderate intellectual disabilities, with accompanying language impairment; however, much variability is observed across individuals. In many cases, individuals with ASD show a characteristic discrepancy between verbal and nonverbal IQ rather than a global impairment across all areas of cognition [43–47]. A pattern of stronger nonverbal reasoning, relative to verbal reasoning, occurs in some individuals with ASD and is often considered to represent the prototypical autism presentation. In comparison, another distinct cognitive profile is characterized by average or above IQ and language abilities, in the absence of an early language delay, and associates with Asperger's syndrome [48]. A third cognitive profile is characterized by a relative weakness in nonverbal and/or spatial reasoning skills as compared to verbal reasoning skills. This cognitive profile often associates with nonverbal learning disability profile that involves relative weaknesses in mathematics achievement and face processing, and may occur in individuals with autism or Asperger's syndrome [49]. Moreover, some individuals with ASD score within the gifted or superior range on tests of verbal IQ, nonverbal IQ, and/or math and reading achievement [50]. Although initial research findings insinuated that these distinct cognitive profiles might lend themselves toward ASD subtyping and distinguishing between Asperger's syndrome and high-functioning autism, the majority of the evidence does not support such a distinction and, instead, supports the idea that language and cognitive abilities or impairments in ASD are best represented along a continuum [47, 51–55].

Individuals with ASD can also exhibit peak cognitive skills which represent strengths above and beyond their other abilities [56] and which provide another means of classification. For example, hyperlexia, or the ability to decode words, emerges at a very young age in some children with ASD in the absence of teaching or instruction [57]. Other peak skills may include those that rely on enhanced perception, including musical talent and strengths in visual-spatial processing and rote memory [58]. Examining subgroups of individuals with particular peak skills may lead to hypotheses or insights regarding the nature of ASD-related information processing abilities and their underlying neurobiological processes [56, 59].

Subtyping ASD According to Genetic and Medical Conditions

ASD arises from a multitude of causes and can be grouped according to etiological subtypes. Investigations into the genetics of ASD have shown that up to 20 % or more of individuals have been identified as having a genetic or genomic disorder and that over 100 known associations exist, which also overlap with known causes of intellectual disability [60••]. One of the most common genetic disorders associated with autism is fragile X, although various other single-gene mutations, rare copy number variants, and even the combined effects of common genetic variants are also associated with ASD [60••, 61]. These genetic abnormalities or variations do not always result in ASD, and instead can be associated with other neurodevelopmental disorders, including intellectual disability without ASD, social and peer-related difficulties that do not reach the level of ASD, and, in some instances, anxiety, depression, or psychotic symptoms [62, 63]. Given this variability in phenotypic outcomes, which can result from the same genetic or chromosomal abnormality, scientists have suggested that environmental factors (e.g., exposure to toxicants, malnutrition, and the in-utero environment) may moderate the risk for ASD [64, 65]. Further, some researchers have suggested that the phenotypic "outcome" of gene disorders should be investigated at the level of the brain [66] and that ASD neurologic subgroups should be the primary focus of study [67, 68].

ASD may also be grouped according to the presence of peripheral pathophysiology that impacts gastrointestinal or immune functioning. The presence of gastrointestinal and feeding disorders in ASD has been recognized since Dr. Kanner's early descriptions, which documented feeding difficulties, severe vomiting, and, in one child, the need for tube feeding [1]. The study of gastrointestinal disorders represents a novel area of inquiry, along with investigations of sleep, obesity, and immune function [69, 70, 71•], and has begun to provide insights into the pathophysiology of well-defined ASD medical/genetic subgroups [72, 73].

Further Subtyping ASD Based on Co-occurring Symptoms of ADHD, Disruptive Behaviors, Anxiety, and Depression

Difficulties with attentional and emotional regulation are commonly observed in individuals with ASD, leading to the identification of subgroups with co-occurring psychiatric symptoms or disorders [74–77]. Although the DSM-IV specified that an ASD diagnosis occurred apart from other childhood-onset disorders such as attention-deficit hyperactivity disorder (ADHD) and social anxiety disorder, systematic studies have shown that co-occurring symptoms or conditions are observed in individuals with ASD and are often the primary focus of clinical care [78–80].

ADHD and Disruptive Behaviors Using standardized assessments, researchers have found that one-third or more of individuals with ASD also meet criteria for formal ADHD diagnosis, and that the most common ADHD subtypes are the predominantly inattentive type and the combined type [80, 81]. Additionally, disruptive behaviors frequently manifest themselves in individuals with ASD. Recent investigations have found that up to sixty percent of adults with ASD and an intellectual disability present with difficult-to-manage behaviors, including self-injurious, disruptive, and destructive behaviors. [82]. In addition, a significant number of very young children present with difficult-to-manage behaviors, whereas oppositional and defiant behaviors can occur in children and adolescents [83–86]. Additional clinically relevant subgroups are comprised of individuals who exhibit behaviors that pose a serious safety risk, including elopement, pica, and self-injury [87–90].

Anxiety Anxiety symptoms also frequently co-occur in ASD and are one of the top treatment concerns of parents and clinicians [91]. Parents report a high level of anxiety symptoms experienced in relation to their child's inability to accept changes in daily routines, to transition from one activity to another, to accept redirection away from perseverative behaviors, or to tolerate environmental stimuli such as particular sounds [92, 93]. Parents also report the presence of anxiety symptoms that seem unrelated to core ASD symptoms, including specific fears, social phobia, and obsessive-compulsive behaviors [94]. Despite emerging evidence that an anxious subgroup exists within ASD, diagnostic uncertainty stems from the lack of validation of traditional measures of anxiety in the ASD population and the concern that core ASD symptoms are indistinguishable from anxiety symptoms [95–98]. Nevertheless, the preponderance of evidence suggests that anxiety disorders co-occur in a substantial proportion of individuals with ASD and represent a clinically relevant subgroup [99].

Depression and Catatonia Individuals with ASD experience major depression and may be particularly at risk when a strong family history of depression exists. The prevalence of depression in ASD is unknown, however, due to the lack of reliable and valid assessments that might distinguish core ASD symptoms from those related to depression [100, 101]. This diagnosis in ASD is further complicated given that symptoms of depression may vary with cognitive and language ability levels, that personal insight may limit the usefulness of self-report, and that environmental factors such as low levels of environmental enrichment or an absence of social support may contribute to the overall presentation [102]. Case studies of individuals with ASD documenting response to treatment of depression and examination of suicidal behavior provide strong evidence that depression and ASD co-occur and that the identification of depressive subgroups within ASD is of paramount importance [103, 104]. Individuals with ASD may also present with catatonia. The origins of this condition in ASD are unknown, and there is no clear evidence that it is associated with mood or psychotic symptoms [105]. Catatonia, therefore, is listed as a specifier in the DSM-5 and is considered a "primary" disorder rather than a symptom of a mood or psychotic disorder [106].

Treatment Research and ASD Subtypes

Our desire to identify ASD subgroups stems not only from the need to understand etiology and cause, but also the need to develop a personalized medicine approach to treating core and associated symptoms of ASD [107–109]. In treatment research, the need to study well-characterized and specifically chosen subgroups in order to increase statistical power and to allow testing of specific hypotheses has led to the recommendation that treatment subgroups be chosen to maximize homogeneity in ways that best illuminate treatment efficacy [109]. Based on these ideas, model treatment approaches are often developed first on a specific subgroup, and follow-up research studies are conducted to determine the generalizability of these treatments to new samples or settings. Thus far, research shows that well-designed behavioral, educational, and pharmacologic interventions can result in significant improvements in the social and behavioral functioning of individuals with ASD, although outcomes do vary substantially.

In early infancy treatment research, at-risk siblings are the most commonly studied subgroup, with an eye towards identifying early signs of risk and providing the earliest possible intervention. Treatment for these at-risk infants often follows an infant mental health model, but the outcomes of such treatments are not yet known [110]. For toddlers and preschoolers, eligibility for treatment research may not be

restricted to particular subgroups, as developmental profiles and ASD severity may change rapidly with treatment and parent factors may be equally important as child factors in predicting outcomes at this age [111–114].

Treatment research that targets difficult-to-manage repetitive behaviors or co-occurring behaviors such as externalizing or internalizing psychological problems may require the presence of minimum levels of the targeted clinical issues [115]. Thus, by design, these studies are targeting clinically defined subgroups. Some treatment approaches may be applied regardless of age or cognitive level (e.g., applied behavior analysis and pharmacological interventions), whereas treatments targeting the development of self-regulatory or social skills may have minimum cognitive or language level requirements [116–118]. With regard to the educational setting, cognitive ability and/or level of academic achievement, as well as severity of externalizing behavioral symptoms, may guide placements [119]. In comparison, adult-oriented treatment research may focus on subgroups of varying cognitive abilities or may focus on dividing groups according to adaptive behavior skills and the level of support required for managing day-to-day life [82, 120].

Although careful selection of treatment study subgroups may lead to interpretable study outcomes, one of the greatest limitations of these studies is the dearth of well-validated dimensional assessments. Further, even when well-validated questionnaire data or clinical ratings of behavior are available, they often provide imprecise measures of behavioral change. The development of mobile technologies and assessments holds the promise of providing an improved method for measuring change in core and associated ASD symptoms within both the home and community settings [121].

Conclusion

The dimensional assessment of core ASD symptoms and the identification of psychiatric, genetic, and medical subgroups contribute to our understanding of ASD complexity. Dimensional measures provide the advantages of precise quantification of the core ASD constructs, increased power for developing statistical models, and accurate measurement of behavioral change. In comparison, the identification of ASD subgroups based on the presence of co-occurring conditions has implications for both research and clinical practice. For research endeavors, the investigation of homogeneous ASD subgroups provides cost- and time-efficient ways of examining ASD-related biological mechanisms and leads to streamlined interpretation of study outcomes in treatment research [122•]. Similarly, for clinical endeavors, consideration of co-occurring conditions is critical to developing personalized treatments. The current state of our scientific knowledge of ASD allows both dimensional and subgroup characterization; the use of standardized assessments to achieve such characterization will lead us toward the ultimate goal of developing personalized care pathways that will be informed by advances in cognitive, behavioral, and medical science.

Compliance with Ethics Guidelines

Conflict of Interest Opal Ousley and Tracy Cermak declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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