Deconstructing autism spectrum disorders: clinical perspective

Roberto F. Tuchman

Summary. Autism spectrum disorder (ASD) is a term used to describe a heterogeneous group of children whose behaviorally defined characteristics overlap with the clinical manifestations of a variety of distinct behaviorally defined developmental disorders. ASD has many etiologies and strong but complex genetic and molecular underpinnings supporting genetic and phenotypic heterogeneity. Clinical and biological heterogeneity in ASD is consistent with the view of autism spectrum disorders as the expression of atypical brain development resulting in variable clinical manifestations that reflect differences in specific genetic and molecular pathways. It is likely that there are risk genes and early environmental risk factors for ASD that contribute to an altered trajectory of brain and behavioral development. These alterations are hypothesized to lead to altered social interaction and consequently to abnormal development of the neural networks critical for social and communicative interaction. This amplifies the abnormal socio-communicative developmental process leading to the full ASD syndrome. The hope is that interventions can alter these early developmental processes and put an infant back on a more typical developmental trajectory. In this discussion an overview of the limitations of the triad of behaviors used to diagnose ASD, specifically from the perspective of how these issues impact diagnosis and treatment of children with ASD will be presented and the clinical boundaries of the autism spectrum will be explored.

Key words. Autism. Cognition. Genetics. Phenotype. Social.

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Introduction

The *Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision* (DSM IV-TR) [1] and the 10th edition of the International Classification of Diseases (ICD 10) of the World Health Organization [2] use the terminology of Pervasive Developmental Disorder (PDD) to categorize children with qualitative impairments in three behaviorally defined domains, reciprocal social interaction, verbal and nonverbal communication, and restricted and repetitive interests. The behavioral criteria used to define PDD have changed and have been refined over the years. In addition in an attempt to advance research and facilitate educational, behavioral, and medical interventions for children with this heterogeneous group of disorders subtypes were developed [3].

The five subtypes under the present DSM/ICD diagnostic schema are:

- *Autistic disorder or childhood autism*, which is the classic group of children described by Kanner in 1943 [4].
- *Asperger syndrome* [5] in which IQ is greater than 70, language development is normal, and social impairments are less severe [6-8].
- *Pervasive disorder not otherwise specified or atypical autism* [9], a disorder in which the lack of an operational definition makes it problematic to classify and study [10-12].
- *Childhood disintegrative disorder* [13-17] in which children have a late-onset autistic and cognitive regression that can include language regression, motor regression, and loss of bowel and bladder use, all usually occurring after age three.
- *Rett disorder*, a neurodevelopmental disorder in which mutations in *MECP2* accounts for the distinct clinical phenotype seen in this group of girls [18].

DSM/ICD criteria for subtypes of autism are based on the number and distribution of behavioral descriptors and do not take into account quantitative differences in symptom severity in each of the individual dimensions. The differentiation of a child with disintegrative disorder or of a girl with Rett disorder, based on the specificity, severity of symptoms, and their developmental trajectory, from the other three subtypes of PDD, is relatively straightforward. In addition both Rett and childhood disintegrative disorder are rare disorders that account for a small proportion of children falling under the spectrum of autism [19]. The differences and boundaries of autistic disorder, pervasive developmental disorder not otherwise specified, and Asperger disorders are not well delineated [20-22]. The term

'autism spectrum disorder' (ASD) is commonly used both by clinicians and researchers to group these three overlapping subtypes.

The DSM/ICD diagnostic schema for children with autism and related disorders has been useful for broad classification and general educational and behavioral interventions. The broadening of the diagnostic criteria used to diagnose children on autism spectrum and the increased awareness and recognition of the importance of social communication skills to daily function by professionals and the public, as well as access to efficacious interventions has played a major role in the increased number of children being diagnosed with ASD [23]. This has been beneficial in terms of governmental and non-governmental agencies investing in research and services for individuals with ASD [24]. On the other hand, the heterogeneity of the disorders classified under the term PDD and the heterogeneity and overlap of the symptoms that defines the subtypes of ASD challenges the usefulness of the DSM/ICD schema. The categorical diagnostic schema for the diagnosis of ASD in the DSM/ICD has raised the concept in the public's mind of ASD as a unifying neurological disorder. This concept of ASD as a diagnostic unifying entity has brought misguided increased pressure to find 'a cause' and a 'cure' for ASD [25].

The DSM/ICD and the comprehensive diagnostic scales such as the Autism Diagnostic and Observation Scale (ADOS) and the Autism Diagnostic Interview (ADI) [26,27], have facilitated progress in the understanding of the autism spectrum nevertheless a significant number of diagnostic controversial issues remain [28]. It has been suggested that our current approach to the diagnosis and treatment of heterogeneous developmental disorders such as ASD needs to be redefined and conceptualized from an interdisciplinary developmental perspective [29]. In the discussion below an overview of the limitations of the triad of behaviors used to diagnose ASD will be presented and the clinical boundaries of the autism spectrum will be explored. These issues will be discussed within the context of clinical developmental neurology, specifically from the perspective of how these issues impact diagnosis and treatment of children with ASD.

The limits of the triad

Over the past two decades research has established that there are numerous etiologies for autism spectrum disorders [30], with strong but complex genetic and molecular underpinnings supporting genetic and phenotypic heterogeneity [31]. Clinical and biological heterogeneity in ASD is consistent with the view of autism spectrum disorders as the expression of atypical brain development resulting in variable clinical manifestations that reflect differences in specific genetic and molecular pathways. It is a combination of complex genetics and environmental influences that shape the distinct but overlapping brain networks responsible for the heterogeneity of the ASD phenotype [32]. A message both from clinical practice and research is that ASD does not have a single etiology or unifying explanation [33]. A corollary to this key concept is that there is no one treatment for ASD.

Children who fall under the autism spectrum label are heterogeneous in clinical manifestations. This means that one child who meets the diagnostic criteria for autism may have a greater number of behaviors under the social domain reflecting greater impairment in social interactive skills, while another child may display a pattern of mild social dysfunction and greater impairment in repetitive behaviors, yet both meet criteria for ASD. There is a complex interplay between the different dimensions ASD. A recent study found that the social interaction and communication domains are closely interrelated and that anxious and compulsive behavior is associated with current social communication functioning [34]. From a clinical perspective, reciprocal social interaction and communication impairments are almost indistinguishable.

In addition to the complex interplay between the three domains of ASD and specifically the interrelatedness of the social and communication dimensions there is a continuum of the genetics of reciprocal social interaction, which is the core and distinguishing feature of ASD [35]. In the general population social skills plot out as a continuous distribution of abilities and deficits [36-39]. The continuum of social skills in the general is consistent with what has been termed the broader autism phenotype [40]. Studies suggest that there are ' autistic traits' in families of individuals with ASD that are subclinical, which may include all three domains or only one, which index the broader autism phenotype (BAP) [39,41-43]. Furthermore, there is evidence to suggest that the psychological-cognitive profile of adolescents and young adults with ASD extend beyond present diagnostic boundaries and that young people with 'autistic traits' share the same cognitive profile as those with ASD [44].

Despite our present understanding of ASD as both biologically and clinically heterogeneous the

concept of ASD as a triad of behaviors, based on epidemiological work from the 1970s, [45], dominates clinical diagnostic work as well as research endeavors and treatment paradigms. The three domains used to define autism co-occur together at a higher rate than expected by chance [46]. However, genetic heterogeneity between the three domains of ASD exists, especially between social impairments and restricted repetitive behaviors and interests and to a lesser extent between social impairments and communication impairments [47]. In addition, the broad autism phenotype of ASD overlaps with many different developmental disorders. This limits the usefulness of the autism triad at a clinical diagnostic level and raises important questions regarding the usefulness of the ASD label for advancing our understanding of the pathophysiology of autism and as such guiding treatment.

A shift to a conceptual understanding of ASD that accounts for the variation of severity of symptoms among the three domains that define ASD is needed. In this type of approach one would make the diagnosis of ASD and then deconstruct this diagnosis into three separate and distinct domains and assess each domain individually with a dimensional approach that accounts for degree of severity of the impairment of that domain. The reality is that differentiating children with a cluster of symptoms that include qualitative impairments in broad domains of behavior such as sociability, communication, and cognitive flexibility, is subjective and creates artificial boundaries between behaviorally defined entities that share similar genetic and molecular pathways [48]. Conceptualizing ASD as a consequence of variation in levels of dysfunction in the three domains of social impairments, communication impairments, and restricted repetitive behaviors and interests, that have no single genetic, neural or cognitive explanation [49] goes a long way towards clarifying the fuzzy boundaries and limitations of our present classification systems for ASD.

The 4th dimension: intellectual disability

Intellectual disability is not part of the present diagnostic schemas of ASD but it can be considered a 4th dimension in that the most salient group differences in subtypes of ASD are noted when the groups are categorized on IQ [50]. The initial description of the 'autistic triad' found a high correlation with the severity of mental retardation with the vast majority of children with severe intellectual disability manifesting the 'autistic triad' [45,51]. Recent epidemiological studies suggest that approximately 40 to 60% of children with ASD, depending on the subgroups of ASD included, have some degree of intellectual disability [19,52]. The differences between older and more recent studies on the co-existence of intellectual disability and ASD reflects the fact that children with less intellectual impairments are increasingly being recognized as falling under the autism spectrum [53]. In the population of children with intellectual disability approximately 8% have ASD [54] although the proportion of children with ASD among those with both intellectual disability and epilepsy may be as high as 25% [55]. In addition the more you look for autistic traits among populations of children with low IQ the more likely you are to recognize them and in chromosomal and single-gene disorders with low IQ approximately one-third may have the 'autistic triad' [56].

Intellectual ability accounts not only for the differences among subtypes of children within the autism spectrum but is an important factor in moderating the expression of ASD [57-60], as a risk factor for the co-existence of ASD with other neurological disorders such as epilepsy [61], as well as in predicting outcome [62-64]. There is significant controversy regarding the relationship of IQ to ASD. On the one hand there is emerging evidence of a genetic correlation between ASD and IQ, with an overlap between the genetic factors that influence behaviors of ASD and IQ [65]. In addition it has been proposed that in a population of children with ASD and epilepsy in whom there is a high association with moderate to severe intellectual impairments that there may be common genes and molecular mechanisms that account for both the ASD and the epilepsy [61]. On the other hand it has been proposed that the common association between intellectual disability and autism is not secondary to common causes but that instead in the population of children with intellectual disability the triad that defines ASD is easier to recognize [56].

There is still allot to be learned regarding the relationship of IQ to ASD and one particular area of research that needs to be expanded is the differences in specific phenotypes between children with intellectual disability and ASD and those with intellectual disability and no ASD. Numerous disorders with intellectual disability and ASD and known genetic deficits have been described and the genes of several of these syndromes have been linked to aberrant synaptic protein synthesis, suggesting a possible common pathway leading to the autism phenotype and cognitive impairment [66]. A common

neurodevelopmental disorder with moderate to severe intellectual disability and the triad of autistic behaviors is fragile x syndrome [67], in which the underlying genetic abnormality is presumed to be a risk factor for the development of ASD [29]. Approximately 30% of males with fragile x have the autism phenotype [68]. Since the protein, FMRP, that is missing or decreased is known, this disorder becomes an excellent example that can further our insight into the development of autism and allows for exploring the question posed above regarding the genetic and molecular differences between those with intellectual disability that develop the ASD phenotype and those who do not. In addition treatment trials of fragile x are now underway and may provide insights into possible therapeutic avenues to pursue in ASD [69].

The boundaries of ASD

There is significant co-existence of the ASD phenotype with multiple genetic disorders [70], metabolic disorders [71], neurological disorders such as Duchenne and Becker muscular dystrophy [72-75], tuberous sclerosis [76-80], sleep disorders [81-86] , epilepsy [87-90] and medical problems such as gastrointestinal dysfunction [91]. There are also significant overlaps between the ASD population and a variety of developmental disorders in which intellectual disability does not play a major role. In this group of behaviorally defined disorders there are social communication impairments that are part of the broader ASD phenotype. This spectrum of social communication disorders includes many common disorders of attention, language, motor function, and specific aspects of cognition.

A common behavioral disorder associated with social communication deficits is attention-deficit/hyperactivity disorders (ADHD) [10,92-96]. Recent studies have shown that there are more symptoms of autism in children with ADHD than in their siblings or in typical developing controls and that this is particularly increased in the subtypes with increased prevalence of other behavioral disorders such as oppositional defiant or conduct disorder and in those with language disorder, motor disorder or increased neurodevelopmental difficulties [97]. This group of children is similar to children described in the 1980's with attention, motor control and perception difficulties (DAMP) [98,99]. The overlap between ADHD, motor symptoms, language and social impairments has been widely recognized [92,100-103].

The overlap of ASD with developmental disorders of language has been historically an important subject of interest and research [104-106]. In the younger child first presenting with a language disorder severely affecting receptive language and who has no expressive language the differentiation at a clinical level of a diagnosis of severe expressive-receptive language disorder versus ASD is extremely difficult, especially in light of the fact that the child might have both diagnosis. It is now recognized that there are different types of language disorders in autism [107] and that significant genetic overlaps between ASD and disorders of language exist [31,108]. The importance of recognizing and describing language subtypes in children with ASD has been underappreciated. For example, there is a subgroup of children who have not been adequately described but who are clinically recognized, with a specific predominantly expressive language, verbal dyspraxia, and with significant repetitive behaviors that overlap with ASD. The importance of recognizing this group of children is that the intervention in regards to their language disorder is different and more language specific than the educational and behavioral for children with ASD. In addition there are specific genetic implications to language subtyping in ASD [109].

A specific group of children who fall under the social communication spectrum are those with semantic-pragmatic language deficit disorders. This group of children initially described in the 1980s has difficulties with the semantic and pragmatic use of language and although not meeting the full criteria for ASD, have socio-communicative deficits that overlap with those of ASD [110]. Deficient pragmatics meaning the communicative use of language, especially nonverbal pragmatics, characterizes children with ASD [111]. Semantic-pragmatic issues are common in high functioning individuals with ASD including those with Asperger syndrome [112-114]. It has been suggested that children whom in the past were classified as having developmental language disorders, especially those in whom pragmatics is affected would presently be classified with ASD [115].

Another common clinical example of what are considered distinct clinical entities in which socio-communicative deficits exist and overlap with ASD are the learning disorders with social deficits [116]. This group of learning disorders has been termed right hemisphere syndrome or the syndrome of nonverbal learning disability (NVLD) [117,118]. Children with NVLD have attention and social communication problems, as well as neuropsycho-

logical profiles that that overlap with Asperger [119]. Children with Asperger and children classified as having high functioning autism, with IQs greater than 70 with adequate communication skills may be difficult to differentiate clinically from children classified as having NVLD or semantic-pragmatic language disorders.

Asperger and other high functioning children with ASD, those with NVLD, DAMP, and semantic-language pragmatic disorders all overlap with Tourette syndrome [120-124]. Tourette syndrome has been associated with ASD since the 1960s [125]. This association was subsequently expanded on by clinical studies showing an overlap between the two disorders and suggesting a relationship in common neural circuitry and genetics [126]. Recently Tourette syndrome has been linked with *CNTNAP2* (*contactin associated protein-like 2*) [127,128] and with *neuroligin 4*, a gene which has been linked to ASD [129]. In addition obsessive-compulsive disorder has also been linked to ASD [130] and the combination of Tourette syndrome, ASD and bipolar disorder has also been reported to co-occur at a higher rate than expected by chance.

The heightened risk of ASD in families with traits such as attention deficits, hyperactivity, impulsivity, motor coordination, language disorders, motor tics, repetitive behaviors and obsessive compulsive disorders, among others, provides clear evidence for multigenic influences in children with ASD [48,131-133]. Discoveries highlighting the overlap at a genetic level between disorders of social communication and the broader ASD phenotype are rapidly expanding as for example in the emerging evidence to suggest clinical, biological, and genetic links between ASD and schizophrenia spectrum disorders [134]. There is also evidence that the *Met* gene is a risk factor for both ASD and gastrointestinal dysfunction [135]. This suggests that not only are there many risk genes for autism but that individual risk genes may account for multiple co-existing conditions with the ASD phenotype.

The role of specific genes such as *FOXP2* associated with language development and in the regulation of *CNTNAP2* [136] may be illustrative example of how risk genes may account for multiple autism phenotypes and how they may relate to the process in brain development responsible for the ASD phenotype. *CNTNAP2* was initially identified in a population of Amish children with a phenotype that include intractable seizures, regression in language and behaviors consistent with the autism phenotype [137]. *CNTNAP2* is a common risk gene for autism [138, 139], is associated with language development [136], Tourette syndrome [128] and schizophrenia [140]. *CNTNAP2* is enriched in highly evolved, anterior regions of the developing human cerebral cortex that overlap with circuitry involved in the development of joint attention [141]. Joint attention refers to the capacity of individuals to coordinate attention with a social partner in relation to some object or event [142] and is a critical early socio-communicative skill that predicts development of language skills. This suggests that social and communication deficits in ASD may arise from common dysfunction of early developmental processes.

Reconstructing autism: developmental perspective

The autism phenotype is present in multiple different types of neurological and medical conditions and the boundaries that define ASD overlap clinically and biologically at the level of multiple genes and common pathways with a multitude of developmental disorders affecting brain function. There is no unitary clinical or biological explanation that characterizes ASD and no single treatment for ASD is to be expected. The overlap of ASD with what are considered distinct neurodevelopmental suggests that multiple genes and complex overlapping pathways are involved in the development of ASD. There is a need to understand the relationship of cognition as indexed by IQ and functional skills with the social communication impairments that characterize ASD both at a clinical and molecular level [143]. We need to address the question of why some children with disorders such as fragile x syndrome develop the ASD phenotype and some do not and address how intellectual disability modulates the expression of the ASD phenotype. The heterogeneity that defines ASD is a challenging obstacle to research on the pathophysiology of ASD.

A research method of trying to create more rigorous behavioral sub-grouping, decrease heterogeneity and gain an understanding of the pathophysiology of the ASD is the use of intermediate traits or endophenotypes. Endophenotypes are biological markers that have genetic underpinnings and are useful in bridging the gap between phenotype and genotype [144]. Biological markers that are being explored, as possible endophenotypes in ASD are neurophysiologic risk indices such as event-related potentials (ERPs) to faces and to speech sounds and atypical brain growth as indexed by structural and chemical brain imaging [145]. There is also an important research shift from categorical to dimen-

sional classification and understanding of ASD. Development of scales that capture the individual differences between children with ASD are critical to understanding the pathophysiology of the different autism phenotypes and in directing behavioral, educational and pharmacological interventions [146]. Categorical measures of children with ASD such as the ADOS and ADI may not be as useful as behavioral scales measuring the dimensionality of the autism phenotype [36,133,147-151]. It is important that research studies not simply use diagnostic schemas such as DSM/ICD or categorical scales such as the ADOS and ADI to classify the groups studied and instead to carefully specify and describe the focus of study.

The clinical assessment from a diagnostic and treatment perspective requires consideration of ASD as a continuum of deficits within the three domains of the autistic triad. In addition level of intellectual ability is a critical dimension of ASD that affects intervention and prognosis. From a research and clinical perspective we need to focus on the developmental processes that precede the full-blown syndrome of ASD and to conceptualize how early recognition of these signs allows for a more rational approach to the conceptualization of ASD and to the clinical management of this group of heterogeneous disorders. A developmental neurology point of view, that focuses on identifying the basic building blocks of reciprocal social interaction and develops tools that can measure these constructs, would allow identification of risk genes and for mapping these discreet aspects of social cognition onto neural networks. Neural networks for social communication involve the complex interplay of hundreds of neurons, interconnecting synapses, neurotransmitters, neuromodulators, the control of genes that turn on and off in orchestrated sequences. The strength of interconnecting synapses is not fixed [152]. The plasticity of complex widely distributed brain networks accounts for the profound effects of the unique environmental influences. Identification of risk genes for ASD [153] offers the hope that the regulation of expression of these genes on synapse development may be modulated and the developmental trajectory of an infant at risk for ASD be positively impacted [154].

The early behaviors characteristic of impairments in the social domain include a number of non-verbal communication skills such as eye-to-eye gaze, and facial and gestures to regulate social interaction such as affective reciprocity, characterized by the reciprocal orienting and exchange of emotional signals between caregiver and child, in addition not responding to name and not pointing are all early indicators of social communicative impairments [155]. Several investigators are currently engaged in longitudinal studies of high-risk infants with older sibling diagnosed with an ASD. The 'baby sibs' studies are identifying the pre-ASD behavioral profile of at risk infants and toddlers and these studies suggest that by 12 months of age some of the siblings who are later diagnosed with autism may be distinguishable from unaffected siblings and from controls at low-risk for autism [155-160]. These studies offer a unique opportunity to study how the ASD phenotype is constructed from a developmental perspective. Dawson [145] has postulated that there are risk genes and early environmental risk factors for ASD that contribute to an altered trajectory of brain and behavioral development. These alterations lead to altered social interaction and consequently to atypical development of the neural networks critical for social and communicative interaction. Once this process evolves there is a lack of further developmentally appropriate social communicative feedback amplifying the abnormal developmental trajectory, leading to the full ASD syndrome. The hope is that interventions can alter these early developmental processes and put an infant back on a more typical developmental trajectory. How the social, communication, repetitive and restricted behaviors, and cognitive dimensions of ASD develop is crucial to understanding the pathophysiology of ASD. An understanding of the how the ASD phenotype is constructed will have a significant impact on the clinical management of all children with ASD and related developmental disorders of brain function.

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Deconstruyendo los trastornos del espectro autista: perspectiva clínica

Resumen. El trastorno del espectro autista (TEA) es un término utilizado para describir un grupo heterogéneo de niños, cuyas características comportamentales se solapan con manifestaciones clínicas de diversos trastornos del desarrollo, definido por su comportamiento. El TEA se debe a muchas etiologías, y su heterogeneidad genética y fenotípica es consistente con bases moleculares clínicas y genéticas complejas, pero significativas. La heterogeneidad clínica y biológica del TEA es congruente con el punto de vista de que el TEA es la expresión de un desarrollo cerebral atípico que da lugar a manifestaciones clínicas variables, que reflejan diferentes vías genéticas y moleculares específicas. Es probable que existan genes de riesgo y factores precoces del entorno para el TEA que contribuyan a una trayectoria aberrante del desarrollo cerebral y de la conducta. Estas alteraciones llevan, hipotéticamente, a una interacción social alterada y, como resultado, al desarrollo anormal de redes neuronales críticas para la interacción comunicativa y social. Todo ello amplifica el desarrollo del proceso sociocomunicativo anormal, dando lugar a un síndrome de TEA completo. Hay esperanza en que la intervención temprana pueda alterar estos problemas precoces del desarrollo y reconducir al niño a una trayectoria evolutiva más típica. Se discuten las limitaciones de la tríada conductual utilizada para el diagnóstico del TEA, especialmente se presentará una perspectiva de cómo estos resultados afectan el diagnóstico y tratamiento de los niños con TEA y de las fronteras clínicas del espectro autista.

Palabras clave. Autismo. Cognición. Fenotipo. Genética. Social.