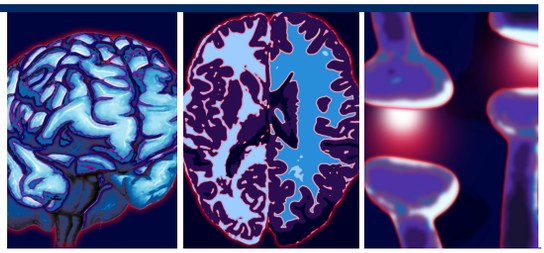
EDITORIAL



Importance of studying heterogeneity in autism

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Among child-onset psychiatric disorders, autism is perhaps the most serious, intractable and challenging to address. One of the factors contributing to this challenge is its heterogeneity observed along a spectrum of pathology [1,2]. The current diagnostic and classification system (DSM-IV) classifies children with autism in one of three subtypes: autistic disorder, Asperger's disorder or pervasive developmental disorder not otherwise specified. However, the inability to establish the reliability and validity of these subcategories empirically is moving the DSM towards replacing the existing subtypes with a severity gradient under the diagnostic umbrella of one autism spectrum disorder [101]. The proposed changes to the way we classify autism may represent a scientific advance in how we might understand this condition, but it is also a sobering reminder that, despite progress, our knowledge about autism is both fragile and sparse.

Categorizing the clinical heterogeneity in children with autism is still of critical importance, regardless of how the DSM changes its definition [3]. Unfortunately, the indicators that we use to represent autism as a heterogeneous condition come from a mixture of fallible inferences and observations vulnerable to error – both systematic and random. Our failure to identify valid and reliable biological markers or other indicators less prone to error represents a serious impediment that needs to be addressed in future autism research. Therefore, we argue here that a better understanding of heterogeneity in autism itself could generate useful information for the study of etiology, diagnosis, treatment and prognosis of the disorder [4].

But what do we mean by heterogeneity? Heterogeneity denotes diversity or variability; it describes dissimilar parts that are somehow connected. We think of autism as a disorder that causes deficits in patterns of cognitive, emotional, behavioral and social functioning that are manifested differently across subgroups of children.

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This generic, lay definition of heterogeneity provides a descriptive foundation for building a scientific framework to systematically study heterogeneity in autism. First, autism can be associated with a diversity of functional qualities; in other words, some children with autism are verbal and others are nonverbal, some have a high IQ and others have a low IQ. Second, autism can be conceptualized as symptom configurations from different domains, exhibiting different severity levels; in other words, some children with autism have severe social communication deficits, mild fixated interests and repetitive behaviors, and other children exhibit the reverse profile. Some children present with 'comorbid' or 'associated' symptoms (anxiety and attention deficits, among others) while other children primarily exhibit only core autistic symptoms [5]. Third, contrary to previous theories, recent findings show that autism is a disorder resulting from diverse causes; in other words, updated genetic findings identify multiple genetic variants both at the same and different loci as being associated with autism [6], and recent twin studies suggest that, in addition to genes, environmental factors play an important role in the causal mechanisms of the disorder [7]. Fourth, autism is perhaps a classic example of a heterogeneous disorder in which dissimilar parts are somehow connected; in other words, despite the differences described above (functional qualities, symptom type and severity, and causal factors, among others) autism is still viewed as one entity, with all affected individuals placed within a spectrum of pathology – autism spectrum disorder [101]. Therefore, the widely accepted (but understudied) picture of autism as a heterogeneous disorder appears to be a valid one. Interestingly, at a time when scientists and policy makers are discussing the idea of personalized medicine for other disorders [8], clinicians and therapists of children with autism are still having a very hard time answering pressing questions from parents related to individualized treatment and specific outcomes. Although we know there is variability in prognosis, in a comprehensive review of early intervention studies, Warren *et al.* concluded that our ability to predict response to treatment and outcome is currently very limited and warrants further investigation [9].

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We believe the time is right for a more scientifically rigorous approach that will lead to a better understanding of autism heterogeneity. Such an approach would not be based on the arbitrary classification of static diagnostic subtypes, but rather on the systematic evaluation of the clinical and research utility of phenotypic and genotypic markers that vary across subgroups of children. This will be of particular importance as we move into a new generation of autism research studies. After decades of research using single-method/design case studies, we now find ourselves entering an era of autism research with large, costly studies involving multiple methods and technologies (phenotypic, cognitive/experimental, genetics, epigenetics, genomics, neuroimaging, pharmacogenetics and randomized control trials, among others); these studies are aiming to not only describe the clinical picture, but also understand the underlying mechanisms associated with causation, manifestation, development and response to treatment in individuals with autism [10].

Although notable progress has been achieved, the integration and interpretation of data from multimethod, multidesign studies of autism has proved to be a major challenge. As a general rule (that could of course be confirmed by a limited number of exceptions) these ambitious research studies have 'failed' to find strong and/or replicable effects. Some of the usual explanations for this phenomenon are related to methodological issues (small sample size, assessment and measurement, among others) that become even more complex owing to the heterogeneous nature of the disorder. We think a new research paradigm is needed as we move forward: rather than conducting studies that compare 'autism cases' with 'typically developing individuals' we have to focus on understanding the meaning of individual and subgroup differences within the autism spectrum. For this new research paradigm to be successful, future studies must focus on the development and evaluation of appropriate measures that could be used to operationalize autism as a heterogeneous entity, and collect data to evaluate the reliability, validity and utility of this new conceptualization of autism. Such measures need to be equivalent across subgroups of interest (i.e., children and youth, males and females, verbal and nonverbal, and severe and mild cases of autism); these measures also need to be sensitive to change and have the ability to capture possible treatment effects.

In closing, we highlight the importance of studying heterogeneity in autism itself and

propose a conceptual and methodological shift to future research: instead of viewing heterogeneity as a *post hoc*, observable outcome of our generic measurements (most of which were originally designed to distinguish autism from non-autism cases), we believe heterogeneity could provide a general framework that will guide the development, implementation and interpretation of new study designs and measurements and that will have the ability to capture individual and subgroup differences within autism. Ultimately, these differences should be robust enough to provide informative 'links' between the different levels of autism – in other words, phenotype and genotype – and account for a substantial amount of the variability observed in studies of autism causes, diagnosis, treatment and prognosis.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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