CROSS TALK

Debating the merits of 'autism' as a diagnostic category

BY **GREG BOUSTEAD**

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In December, in **an editorial** published in the journal *Trends in Neuroscience,* **Eric London** brought a megaphone to a provocative question that has been whispered among researchers in the field for years: Does the term ‘autism’ really hold value? In a **follow-up Q&A** on our site, London clarified his argument: “It would be great if categorical diagnosis worked, but it doesn’t.” However, if we doaway with autism as a diagnostic term, what should replace it? We asked several scientists with expertise in basic research, translational medicine, clinical research and policy to weigh in on the topic.// //]]>

Thomas Insel

Director,National Institute of Mental Health

A single diagnostic bucket is problematic

***Thomas Insel**, a physician and neuroscientist, is director of the National Institute of Mental Health in Bethesda, Maryland.*

In many fields of medicine, from oncology to infectious disease, there is a growing realization that the pathway to better treatments runs through better diagnosis. ‘Precision medicine’ is the term used to describe the process by which ostensibly singular syndromes, such as breast cancer or

pneumonia, have been deconstructed into a multitude of diseases with specific treatments for each.

Oddly, in autism, the process has moved in the opposite direction, as many forms of autism are now clustered together underthe term ‘autism spectrum disorder.’ The move away from precision medicine might make sense given our limited understanding of how to deconstruct autism and, more importantly, the lack of treatments for potential subtypes of thedisorder. A catchall term like autism spectrum disorder simplifies coding, billing and many aspects of service delivery.

But a single diagnostic bucket for a multitude of disorders introduces problems for scientists, especially when researchers are under the belief that the diagnosis confers validity as well as reliability. This is the reason for the National Institute of Mental Health’s **Research Domain Criteria** (RDoC) project: Diagnosis based solely on signs and symptoms is unlikely to be a valid reflection of a precise biological disorder.

Indeed, virtually every field of medicine has developed **biomarkers** to augment diagnosis. The challenge for scientists studyingautism is to deconstruct autism spectrum disorder into its many subtypes by identifying biomarkers, including cognitive factors, that can reveal valid subtypes.

It is important to understand that a useful biomarker does not need to be abnormal in every person within the broad autism spectrum disorder category. In fact, the point of having a biomarker or cognitive marker is to identify more homogeneous subgroups. Even in the near term, the RDoC a pproach can reveal subgroups of autism that reflect mechanisms underlying thedisorder or predict clinical response.

Again, this is the lesson from other areas of medicine. When only half the children with fever and sore throat have a positive Strep culture, we don’t throw out the culture results.

Precision medicine becomes most important for designing clinical trials. No one would launch a trial of a new antibiotic for all children with fever or all adults with chest pain, unless the goal was limited to short-term symptomatic relief. For thedevelopment of effective treatments, biomedical or psychosocial, we need to select individuals with the same disorder.

In terms of treatment response, we don’t yet know whether autism is 5 or 50 disorders, but starting with a highly heterogeneous population is destined to yield negative or weak treatment effects. Defining a more precise diagnosis, as planned through RDoC is, therefore, the first step to developing more effective treatments.

Celine Saulnier

Clinical Director for Research,Marcus Autism Center at
Children's Healthcare of Atlanta and Emory University in Atlanta

We need common ground across clinical, scientific domains

Celine Saulnier *is clinical director for research of the Marcus Autism Center at Children's Healthcare of Atlanta and Emory University inAtlanta, where she is also assistant professor of pediatrics.*

The debate about whether the current diagnostic criteria for autism spectrum disorder and other neurodevelopmental disorders in the latest edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-5) have both clinical and scientific utility is an important one. I experience this dilemma every day as I straddle both of these worlds, conductingdiagnostic evaluations for clinical research.

If clinical practice generates questions to answer through research, and science is then translated back into enhancing clinical practice, then I believe we need common classification across both domains.

Eric London's paper brings to light the many challenges of trying to squeeze the DSM-based peg into a neuroscience- or research-based hole, resulting in the development of the National Institute of Mental Health's **Research Domain Criteria**(RDoC). But without some common language, criteria and knowledge base across disciplines, splitting off into different paths is not likely to help the cause.

From a clinical perspective, the DSM certainly poses challenges in that behavioral symptomatology is classified into categories — and, as argued by London, often overlapping ones. For autism spectrum disorder, the DSM-5 has improved in taking a more dimensional approach than previous editions (by considering autism a spectrum and removing subtypes that science had difficulty substantiating), but it is still categorical.

Despite the controversy of labels (disorder, disease, condition and so on), we cannot underestimate the need to have adiagnosis for eligibility purposes. In the absence of a diagnosis, individuals are likely to not receive much-needed treatments or interventions to overcome their challenges, nor will they receive insurance reimbursement for care (the need for insurance reform is a separate issue altogether). What's more, if given the wrong diagnosis (even if closely related to other neurodevelopmental conditions), an individual is at risk for receiving inappropriate treatment.

The common thread across all autism spectrum disorders regardless of intellectual ability or

symptom severity is the social deficits. Non-autism neurodevelopmental disorders may have social complications as a result of their core symptomatology, but these vulnerabilities are not primary to the disability. Treating them as such would not be optimal.

As noted by London, we are learning that early predictors of autism in the first year of life (for example, early motor, posturaland sensory processing impairments) can differ from the symptoms typically observed later in development, and they might not be the core and defining symptoms historically characteristic of autism (social communication deficits and restricted and**repetitive beh aviors**).

When social communication impairments are not identified and treated early on, debilitating a ssociated behaviors, such asaggression, self-injury and behavioral dysregulation, can develop, surpassing the disability itself and requiring substantial remediation throughout life.

Collectively, these complexities pose challenges for the application of either the DSM or RDoC a cross fluctuating developmental stages. This also raises the question of whether autism has one etiology or whether ‘autisms’ are the result ofvarious neurodevelopmental pathways going awry at different points in time.

William Mandy

Senior Lecturer,University College London

There is value in a diagnosis of autism

William Mandy *is senior lecturer at University College London, where he practices clinically and conducts research. Much of his work focuses on how autism is best conceptualized.*

Eric London convincingly argues that the diagnosis of autism lacks validity. Current diagnostic criteria for autism almost certainly do not describe a single, real disorder. In fact, they probably don’t even describe a coherent syndrome, but rather conflate at least two symptom dimensions that **can occur independently of each other**.

There are probably dozens, or even hundreds, of autisms that have distinct causes, prognoses and treatment needs, and that only superficially resemble one another.

Nevertheless, despite my lack of faith in the scientific validity of autism, I believe there is value in

continuing to use thediagnosis, both in clinical work and in clinically focused research. Why? Because a diagnosis should be judged by its utility as well as its validity — and over the years, the diagnosis of autism has built up a fair amount of utility.

In part, the growth of its utility is based on a steady increase in public understanding of the disorder. I think many people arealso becoming more empathetic toward people who have the diagnosis. Schools **increasingly accommodate and support**children with autism. Parents feel less blame for their child's difficulties if the child is diagnosed with autism. Also, treatmentsare emerging that help alleviate some of the difficulties experienced by people with autism.

What's more, the community of people with autism is growing in cohesion and strength, and is increasingly finding ways toarticulate the needs of its members. Many people report that receiving an autism diagnosis served to help them better understand themselves, and to view their own struggles with more compassion and less shame. Others report a sense ofkinship with other people with autism that fosters a positive self-concept and greater resilience.

London suggests that autism be replaced with a broader 'neurodevelopmental disorders' category, with specifiers being used to communicate the individual's specific pattern of neurodevelopmental difficulties. In theory, this is an excellent idea but, in my opinion, it is impractical. Such a move would cause widespread confusion in clinics, schools and the wider community — and it would certainly be resisted by the countless numbers of people for whom being 'autistic' is a proud part of their identity.

I believe that we should retain the category of autism, but not its reification. We can continue to use the term autism or autism spectrum disorder, while understanding that it denotes a heterogeneous group of people. The task of the next decade is to discover the best ways of parsing this heterogeneity: Success in this will result in a more valid system for categorizing neurodevelopmental problems. Only once we have at least the beginnings of a scientifically valid replacement should autism be retired from psychiatric classification.

Steven Hyman

Director of the Stanley Center for Psychiatric Research,Broad Institute of MIT and Harvard

Current categories are both too narrow and too broad

Steven Hyman *is director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard University, as well as Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology.*

Diagnostic criteria for autism and indeed all neuropsychiatric disorders remain in an awkward transitional state. Objective medical tests are still lacking, and shortcomings in the newest edition of the “Diagnostic and Statistical Manual of Mental Disorders” (DSM-5) **are well recognized**.

Among other flaws, DSM-5 categories have the odd property of being too narrow and too broad at the same time. Narrowly constructed DSM diagnostic silos create vast erroneous comorbidities even in cases where a single pathophysiological process is likely to be at work. Despite their narrowness, DSM categories do not identify homogeneous populations, as confirmed by recent a dvances in genetics.

Yet current knowledge of pathogenesis — the basis of mature diagnostic systems in medicine — is not yet adequate for autism or other neuropsychiatric disorders to produce a good alternative. The National Institute of Mental Health’s commitment to developing **Research Domain Criteria** (RDoC) centered on the dysfunction of neural circuits is at an early stage. An emphasis on RDoC-like a pproaches already benefits researchers, however, by freeing them from the need to ground their research in fictive DSM-5 categories.

Scientifically, the DSM-5 definition of autism spectrum disorder is an improvement over the previous version, the DSM-IV, by removing poorly validated subtypes. However, the category still selects populations that are too heterogeneous to form thebasis of most brain imaging studies or clinical trials.

Genetics has been successful in the past few years in spite of the DSM. Given the intrinsic heterogeneity of genetic risk for neuropsychiatric disorders such as autism, large samples are needed to achieve results that stand up over time. The fuzzinessof DSM diagnoses makes the ‘signal-to-noise’ problem even worse. Ultimately, the identification of most common and rare genetic variants that contribute to autism will require samples from **many tens of thousands of individuals**.

Strategically, it makes sense to lump neurodevelopmental disorders for now, in order to give researchers a chance to start overagain, free of the bias created by current unwarranted splits. Researchers can then reanalyze these larger groupings with modern scientific tools, to search for meaningful stratification of disorders that might, for example, inform treatment.

One such approach, which is being applied to general medical disorders, is to search within large genetically analyzed populations to **find affected individuals with shared risk factors**. Individuals who thus appear to be stratified by their genetics would then be recontacted by researchers and deeply characterized — perhaps with new approaches suggested by thegenetics.

The ultimate goal is finding empirically based subgroups within larger syndromes.

For now, as researchers test new hypotheses offered by genetics and other scientific observations, there must be some latitude for researchers to leave the Procrustean DSM categories behind. The RDoC initiative is a good start. However, in thelong run, it will be important to bring the sets of criteria together again, or at least to have effective crosswalks.

Individuals with autism and their families will want to know how new scientific findings apply to their condition, most notably to treatment recommendations. Also, if the Food and Drug Administration were to approve a new drug, it would have to rely on criteria used by clinicians, because it is clinicians who will be doing the prescribing. In both cases, it will be critical to be able to connect scientific findings with clinical care.