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LETTER TO THE EDITOR

Is autism a unitary biological entity? A revised and extended response to "A radical change in our autism research strategy is needed: Back to prototypes" (Mottron, 2021, Autism Research)

To the Editor:

The autism diagnosis has expanded significantly. What to do about this expansion depends on whether the clinician or researcher believes the autism diagnosis is capturing a unitary biological entity or is, instead, capturing a segment of neurodevelopmental impairment in the "continuous distributions of risk factors and symptoms in human populations" (Hyman, 2021, p. 14). If the autism diagnosis is a set of symptoms that identify a unitary biological entity, narrowing and clearly specifying autism criteria is important in order to create an autism diagnosis that best reflects the unitary biology of autism.

Mottron's arguments suggest that he, like many other researchers and clinicians, believes autism is a unitary biological entity. Mottron proposed that replacing polythetic DSM 5 criteria with prototypical autism based on expert clinicians' personal autism categories would increase specificity and reduce heterogeneity through limiting DSM 5 symptoms to a smaller set of homogeneous values. Mottron argued that his prototypical autism would provide a more accurate autism diagnosis than the DSM diagnosis criteria, formal diagnostic assessments, or diagnostic screening instruments. Mottron posited that shared, narrowly drawn personal clinical categories are better at identifying autism than fixed criteria because shared clinical categories are the "intersection of maximally resembling exemplars" (Mottron, 2021, p. 3).

However, is autism really a unitary biological entity? In addition, if so, is it a natural kind? Genes and neurons are "natural kinds," the gold standard of science, because they can be seen and measured as unitary biological entities that have stable and wide-ranging predictive powers (Franklin-Hall, 2015). Autism diagnoses do not appear to be either natural kinds or unitary biological entities because they are not stable, discrete, objectively measurable entities and cannot predict the discovery of new biological entities. Instead, an autism diagnosis is more likely to be a pragmatic category aggregating some of the distribution of biological risk factors and symptoms.

Many assume that there are unitary biological pathways that cause autism: each pathway is a pathophysiology of autism. One form of pathophysiology is a predictive line wherein a set of specific gene variants or single gene variant is shown to confer a specific brain impairment in an environmental context that, in turn, is linked to an autism diagnosis.

Much research has attempted to find clear causal lines for autism, but although many gene variants and brain impairments have been linked to autism, no autism pathophysiology has yet been discovered. This is likely to be the result of the immense heterogeneity in gene variants, brain impairments, environmental influences, and comorbidities found for autism (Waterhouse and Gillberg, 2014). While immense heterogeneity is to be expected if autism is a category drawn from a continuous distribution of biological risk factors and symptoms, limited heterogeneity is to be expected if the autism diagnosis is capturing a unitary biological entity.

Mottron sees autism heterogeneity as noise caused by comorbidity. He believes that comorbidity has dissolved autism "into a now uncontrollable morass of heterogeneity" (Mottron 2021. p. 4). Mottron claimed that comorbidity stems from "the trivial discovery of autistic traits in an indefinite variety of psychiatric and neurodevelopmental conditions" (Mottron 2021, p. 4). This argument appears to suggest that if comorbidity could be peeled away, there would be limited heterogeneity and autism would be revealed as a unitary biological entity.

The counter argument is that autism heterogeneity occurs because nearly all cases are unique, and most cases capture a slightly different aggregate of the continuous distribution of biological risk factors and symptoms. Research has found immense heterogeneity and no specific pathophysiology. This suggests that even constructing the narrowest diagnostic criteria will not identify autism as a unitary biological entity, and will not eliminate associated heterogeneity.

In fact, narrowly drawn autism diagnoses impede "clinical early intervention…and research on prevention and early intervention… especially to the detriment of children and adolescents, who often suffer a shifting panoply of symptoms and impairments that do not fit DSM diagnostic silos" (Hyman, 2021, p. 12). The early-in-life application of narrowly drawn autism categories—whether DSM autism criteria, or prototypical autism, or autism diagnostic screening tools—can only create

temporary research samples that do not predict the heterogeneity of ensuing behavior patterns in developmental trajectories. Moreover, many children will only partially meet early diagnostic criteria and will be excluded from study, and put into a "left-over" category.

All heterogeneity is scientifically meaningful and heterogeneity most likely occurs because each case captures a slightly different aggregate of the continuous distribution of biological risk factors and symptoms. This heterogeneity can only be fully explored by dismantling diagnostic categories (Hyman, 2021; Waterhouse and Gillberg, 2014). The field should encourage research that takes autism apart to explore causal patterns within the heterogeneity in non-diagnostic groupings (Waterhouse and Gillberg, 2014).

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