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LETTER TO THE EDITOR

# Response to "A radical change in our autism research strategy is needed: Back to prototypes" by Mottron et al. (2021)

We agree with Dr Mottron that polythetic criteria for autism spectrum disorder (ASD) have resulted in expansion of the autism spectrum, leading to heterogeneity that impedes scientific progress. We further agree that since current diagnostic criteria are vague enough to apply to a range of ages and functioning levels, they lack operationalization and specificity for ASD.

Mottron proposes a two part solution. First is to designate experienced clinical researchers to identify prototypical cases. Those of us with decades of such experience have some sympathy with this idea but there are substantial practical challenges, including determining how someone might qualify as an expert, how such expertise could be trained, and so on (summarized by Gillberg, 2021). Not every case of ASD is diagnosable quickly as should be true of "prototypical" cases (de Marchena & Miller, 2017). Observational instruments such the Autism Diagnostic Observation Schedule-2 (ADOS-2) play a useful role in eliciting responses to uniform social presses, to elucidate the most fitting diagnosis. In addition, tools such as the ADOS and ADI provide separate evaluation for the social and restricted/repetitive behavior domains (RRB's), while single-score questionnaires with a cutoff that combine all elements (such as the SRS) introduce more clinical heterogeneity.

Mottron's second proposal is to create smaller, more homogeneous subgroups, with the aim of increasing the probability of linking phenotypic and biological levels. This approach has been tried many times; these efforts have not generally yielded better correspondence with underlying abnormalities. Rapin (2014) spelled out the difficulty of mapping syndromes defined at one level of description onto syndromes defined at another level (behavior, pathophysiology, etiology).

While increasing within-group phenotypic homogeneity has amplified genetic linkage signals and associations in genome-wide studies, the improvements are modest (Chaste et al., 2015). In addition to subtyping by diagnostic and statistical manual of mental disorders (DSM–5) specifiers (i.e., intellectual and language disorders), Constantino (2021) suggests subtyping by the earliest and most predictive signs of autism, and by familial versus sporadic etiologies. Fein and Helt (2017) suggested phenotypic variables that might better align with biological variables because they are less affected by environmental variation: (1) behaviors that appear in the first year of life; (2) clearly biological or medical processes (e.g., epilepsy, high pain threshold, social improvement with fever, physical growth parameters); and (3) regression in acquired skills without gross environmental changes. They also advocate subtyping by (4) response to intensive early intervention and (5) longitudinal trajectory more broadly.

We would like to highlight a deeper problem not raised in the current discussion: the coherence of autism as a syndrome (Waterhouse et al., 2016). Are the two fundamental aspects of autism (social impairment and RRBs, tightly related to each other, or does each exist independently? In 2014, the journal *Autism* published four papers (by Mandy et al. 2014 and Frazier et al. 2014) addressing the coherence or fractionability of the two domains; no strong conclusion could be drawn from the arguments or the data. Given that virtually all autism studies include participants who meet diagnostic criteria for ASD, they will by definition have deficits in both domains; studying them cannot resolve this issue. One solution is to study youngsters with social disabilities, without regard to RRBs, and then explore the presence, type, and extent of their RRBs, and then do the opposite, starting with children with significant RRB's and then studying their social functioning. Such an enterprise could examine the interdependence of the two domains of impairment and the coherent syndrome status of autism.

Finally, an approach not discussed by Mottron is to start with medically or environmentally mediated etiologies, and then explore the resulting phenotypes. Although the resulting human and animal phenotypes will have varying degrees of heterogeneity, and progress will be slow as neurodevelopmental syndromes are identified, we think that this "genotype first" approach is likely to be highly fruitful in the next period of autism research.

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