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Moving forwards not backwards: heterogeneity in autism spectrum disorders

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7 The article by Mottron and Bzdok¹ argues that heterogeneity in autism is artefactual, and that 8 returning to a "prototypical" autism would benefit clinical practice and research endeavours. We note 9 that the authors do not define what they mean by "prototypical" autism and thus it is left for the reader 10 to interpret who would and would not be included under the authors' revised definition. However, 11 from our reading, we argue that, though perhaps unintended, the suggestion is for a return to a rather 12 stereotyped understanding of autism, one which is no longer fit for purpose and that research does not 13 support: we offer our insights from both clinical and academic practice.

14 A move away from the (assumed) prototypical approach to autism proposed by Mottron and 15 Bzdok¹ has, in fact, only recently taken place. One familiar autistic presentation – that of young males 16 of mid-intellect without neurodevelopmental or mental health comorbidities - has been consistently 17 favoured and has repeated from the original clinical observations of autism² to contemporary research sampling; for example, individuals with comorbid intellectual disability, who have mental health 18 19 comorbidities, or who are female are consistently left out of research samples^{3, 4}. This approach 20 maintains a narrow lens of what autism looks like. It may offer a simpler scientific case, but it is 21 biased, only examining a subsection of the autistic population, and is ultimately invalid. Indeed, the 22 authors' suggestions, if ever implemented, would likely lead to even poorer rates of identification for 23 women and adults who did not have the opportunity to be diagnosed in childhood. A definition that 24 incorporates data from females^{5,6}, adults, people with mental health comorbidities and comorbidity 25 with conditions such as ADHD would contribute to an updated description, and not a less accurate 26 description. Importantly, these updated definitions⁷ provide the basis for better clinical care through 27 the design and refinement of updated interventions, such as for anxiety and depression⁸.

28 Indeed, the current evidence does not support the notion that narrowing our focus will resolve 29 the question of the biological underpinnings of autism. Three previous subtypes of autism under the 30 DSM-IV, PDD-NOS, autistic disorder and Asperger's Syndrome, have more in common in their 31 genetic underpinnings than differences⁹. This does not support the authors' view that one previous 32 subtype is muddying the waters. This also comes in the context of a broader genetic picture, in which evidence suggests shared genetic factors between neurodevelopmental conditions, as well as within 33 them¹⁰. Furthermore, Happe and colleagues¹¹ have demonstrated that the social, communication and 34 repetitive interest symptoms of autism (now considered a dyad of social and non-social impairments⁷) 35 36 have independent genetic bases, and as such individuals are going to vary along three different 37 continua, leading inevitably to a very heterogeneous population.

Mottron and Bzdok¹ complain of shrinking effect sizes in the field. However, we note that as factors such as sample sizes in research studies increase, the uncertainty around effect size estimates will reduce: while this may appear to suggest a reduction in the effect sizes themselves, it may in fact reflect improving precision and reproducibility¹², qualities we feel supersede effect sizes in importance.

43 Where we can agree with the authors is that we (as clinicians and researchers) want valid, 44 specific and reliable diagnosis with high predictive accuracy, and a clear diagnostic threshold, which 45 considers functional impairment, and enables discounting differential diagnoses. Such diagnostic 46 practices are in the best interest of individuals, their families and health services offering support. The 47 authors appear to assume this does not happen in the clinic, but in our experience, differential diagnosis and careful clinical judgment leads. And we are not alone: Molloy et al¹³ report the 48 49 diagnostic practices in their clinic and emphasise that quantitative scores generated from standardised 50 assessment tools such as the ADOS may be helpful, but the activities and interactions that such tools 51 scaffold support clinicians to build qualitative impressions: it is these impressions that make key 52 contributions to a diagnostic decision. Unlike the portrayal in Mottron and Bzdok¹, it is simply 53 inaccurate to suggest that people who score above threshold on the ADOS are automatically granted a 54 diagnosis.

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55 Nonetheless, used as a laboratory test, misclassifications via the ADOS may occur. Here, we 56 argue that assessments used for research purposes only do need to be treated with caution: autism 57 researchers who have limited or no clinical experience may well not have the expertise to make 58 differential diagnoses, and misclassification may have ramifications for the autism samples included 59 in research studies. Perhaps the weight of the dilemma rests within research sampling rather than 60 clinical practice. One suggestion would be for researchers to ensure that their autistic samples have a diagnosis given by an appropriate clinic (for example as done by Underwood and colleagues¹⁴). Of 61 62 course, such studies may replicate the biases and barriers faced by certain groups in achieving an 63 autism diagnosis: an alternative would be to look to population-based studies with more representative 64 real-world sampling (e.g. meta-analyses of clinic and population-based studies suggest many women 65 who meet the clinical threshold for autism do not proceed to clinical services for diagnosis¹⁵). The 66 tensions of ensuring classification accuracy and representation in research will need ongoing 67 discussion in our field. We also recommend that researchers give fuller descriptions of their samples, 68 such as functional ability, mental health cooccurrence, and medication status – to name just a few 69 important variables along which there is much heterogeneity in the autistic population - to help inform 70 future clinical care and scientific understanding.

We sympathise with the frustrations that come with the heterogeneity of autism, and a desire to reduce the complexity surrounding its presentation and aetiologies. But we argue that we should not sacrifice validity for the sake of simplicity, particularly at the personal cost of many people who already face significant barriers to being diagnosed, nor should we assume that the field had autism right the first time: while a prototype is the original, it is also by definition preliminary.

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77 Conflicts of interest

78 The authors declare no conflicts of interest.

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