

Hobson, H and Petty, Stephanie (2021) Moving forwards not backwards: heterogeneity in autism spectrum disorders. *Molecular Psychiatry*.

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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
33 evidence suggests shared genetic factors between neurodevelopmental conditions, as well as within
34 them¹⁰. Furthermore, Happe and colleagues¹¹ have demonstrated that the social, communication and
35 repetitive interest symptoms of autism (now considered a dyad of social and non-social impairments⁷)
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.

38 Mottron and Bzdok¹ complain of shrinking effect sizes in the field. However, we note that as
39 factors such as sample sizes in research studies increase, the uncertainty around effect size estimates
40 will reduce: while this may appear to suggest a reduction in the effect sizes themselves, it may in fact
41 reflect improving precision and reproducibility¹², qualities we feel supersede effect sizes in
42 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
48 diagnosis and careful clinical judgment leads. And we are not alone: Molloy et al¹³ report the
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.

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
61 diagnosis given by an appropriate clinic (for example as done by Underwood and colleagues¹⁴). Of
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.

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

76

77 **Conflicts of interest**

78 The authors declare no conflicts of interest.

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80 **References**

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