

# *Commentary: critical considerations for studying low-functioning autism*

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# Commentary: Critical considerations for studying low-functioning autism

**Bhismadev Chakrabarti** 

Centre for Autism, School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK

Autism research has been on an upward trajectory over the last three decades, evidenced by an approximately 24-fold increase in the number of published papers with the term ‘autism’ as indexed by Pubmed. Notable in this trajectory are two clear trends: (a) a shift from primarily clinical and behavioural reports, to more observational studies that provide alternative measures of the phenotype, such as eye-gaze tracking, neuroimaging, and (b) a shift from primarily phenotypic studies to an increasing number of genetic studies.

Research on the autistic phenotype has focused mostly on higher functioning individuals on the spectrum, neglecting those on the lower end. According to an estimate provided in the target article, based on a public autism research database, approximately 11% of the data come from individuals with a IQ < 85 (Jack & Pelphrey, this issue). This estimate highlights the magnitude of the asymmetry in autism research, and necessitates a direct focus on these understudied individuals. In view of autism spectrum disorders (ASD) as a multidimensional spectrum, choosing how one defines ‘low-functioning’ is the first of many challenges. The authors focus on three features in the current review: that of minimal verbal ability (MV), developmental regression (R), and intellectual disability (ID). Existing reports suggest that 25–30% of ASD individuals show MV, approximately 32% show regression in some form, and approximately 31% have some version of ID. Jack and Pelphrey have systematically consolidated the neuroimaging findings on ASD individuals with these features. In doing so, this review puts a much-needed spotlight on these understudied populations within the autism spectrum.

Importantly, it leads to broad questions about the structure of ASD and the optimal methods to study it.

## Dimensions and categories

A long-standing discussion around dimensions and categories is brought to the fore by this review. Should we be thinking of these different populations (MV, R and ID) as distinct subgroups within ASD? If so, then it raises a question on the nature of overlap between these subgroups. There is likely to be a substantial overlap between these subgroups, with significant noise associated with the subgroup boundaries (due to the diversity of boundary criteria among different studies, as well as measurement

error). Accordingly, any search for markers unique to these subgroups will be particularly challenging and limited in the scope of information it can provide. As highlighted by the authors of the target article and others, there are multiple such potential subgroups within ASD that could be based on developmental profile, sex/gender, clinical phenotype, as well as cognitive profile (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013).

A major part of this challenge comes from the case-control design used in most of the experiments covered by the review. The strength of the case-control design relies heavily on the appropriateness of the matching criteria between the two groups. These criteria ideally should be orthogonal to the measure being contrasted between the two groups. In case of ASD with its potentially multiple subgroups or dimensions, such matching is difficult, if not impossible. A commonly used workaround of ‘controlling for’ variables that the two groups are not matched on is fraught with statistical problems (Miller & Chapman, 2001).

Dimensional approaches have gained in prominence in the last 5 years, especially with the proposal of the Research Domain Criteria (RDoC) framework (<http://rdoc.nih.gov>). While acknowledging the obvious appeal of dimensional models, it is worthwhile to ask questions on the interrelationship of the different dimensions, similar to the question on the overlap of the three subgroups mentioned above. MV can thus be conceptualised as an extreme low end of a continuous dimension of verbal ability, and similarly ID as a low end of a continuous dimension of IQ/related measure. Indeed, the review highlights studies that have identified neural correlates of these dimensions, irrespective of a diagnosis of ASD (Cardy, Flagg, Roberts, & Roberts, 2008; Spencer et al., 2006). In this context, regression provides an interesting contrast to MV and ID, in that it does not directly map onto a similar continuous dimension. The suggestion by the authors of using Childhood Disintegrative Disorder as a distinct subgroup defined by regression before the age of 10 is novel and potentially informative. Additionally, it may be possible to quantify individual variability on regression using a number of indirect variables, for example, magnitude and timing of the loss of abilities.

Most of the evidences discussed in the review uses the prevalent categorical approach. A potential direction for future studies would be to examine

the neurobiology of the associated continuous dimensions, irrespective of diagnostic labels. Such studies would need larger representative samples, where all sections of the distribution are represented (see Figure 1).

From a dimensional perspective, there is a critical need to study the understudied populations identified by the authors, since these represent the extreme ends of different, but potentially overlapping, dimensions. Restricting lab-based studies to only part of a phenotypic dimension (e.g. moderate/high IQ) is unlikely to reveal the nature of its relationship with the underlying biology, which may/not be linear.

### Data-driven and hypothesis-driven approaches

In an era of big data, data-driven techniques have a certain allure. Multivariate techniques, such as clustering, show promise when dealing with the sizeable heterogeneity seen in ASD (Lombardo et al., 2016; Romano et al., 2014). These studies usually need considerably larger samples than the ones currently used in most neuroimaging studies of ASD. Second, such data-driven subgroups may not map neatly on to subgroups based on observable clinical phenotype (e.g. MV, ID, R). There is a need to develop a principled approach to resolve such mapping issues. Third, there are a range of clustering algorithms that are typically used in such approaches, which do not always reveal the same clusters. Such discrepancies lead to the approach not being entirely data-driven.

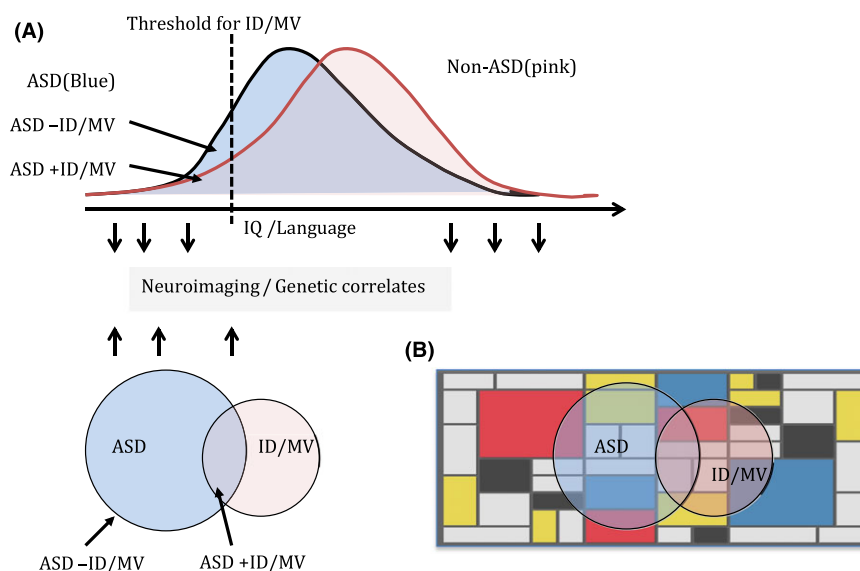
In order to move forward on the study of these understudied populations within ASD, it is essential to clarify if the aim is (a) to find 'homogeneous' subgroups, with no bearing on whether they map onto clinical boundaries; or (b) to determine neuroimaging/genetic

correlates of specific clinically defined subgroups. The second option represents the hypothesis-driven approach that has dominated autism research. If the aim is to specifically understand the neurobiological correlates of MV/ID/R, then a hypothesis-driven approach is preferable; while a data-driven approach might be better suited to examining a large multimodal dataset (e.g. theNDAR database) with no prior hypothesis on the nature or number of subgroups.

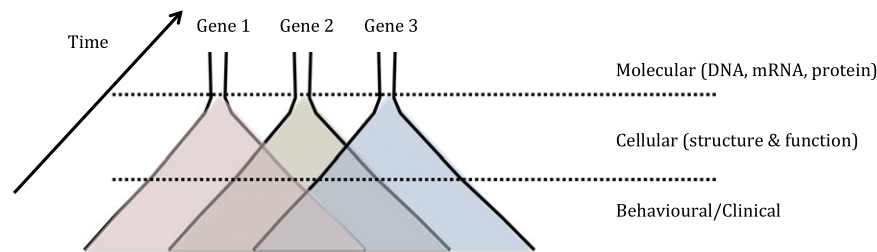
As a future direction, the authors discuss results from several hypothesis-driven imaging genetic studies in humans and animal models that throw light on the underlying biology of these understudied groups. However, neuroimaging phenotypes are unlikely to reliably map directly on to genetic variability, and needs to be considered in combination with measures from different levels and techniques (see Figure 2).

### Neuroimaging and beyond

Neuroimaging is a term that has grown to encompass a wide variety of measures of brain structure and function that include multiple techniques, such as MRI, DTI, as well as MEG, EEG, and NIRS. In this sense of the term, it provides different (endo) phenotypic measures that may map onto different levels (behavioural/clinical or molecular/cellular). Neuroimaging data from the understudied populations within the autism spectrum can make vital contributions to both hypothesis-driven and data-driven studies. In hypothesis-driven studies, such data can help delineate the neural architecture underlying the key dimensions and/or subgroups of interest. In data-driven studies, such data can contribute to building multimodal classifiers, in combination with other data streams, that can help identify subgroups within ASD. The practical challenges of running



**Figure 1** (A) A schematic summary of the dimensional (top) and categorical (bottom) approaches to investigating understudied populations within ASD. (B) The phenotypes (whether conceptualised as dimensions or categories) are likely to map onto a mosaic of genetic variability. Each box in the mosaic can be thought of as the effect of a single gene. ASD, autism spectrum disorders [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**Figure 2** A heuristic to understand the impact of different genes on observed heterogeneities within the autism spectrum disorders phenotype. At a molecular level, the direct impact of genetic variation is on the level of mRNA and protein. Interaction among proteins at a cellular level contributes to cellular structure and function. Cellular interactions at a larger scale, in turn, gives rise to observable behavioural/clinical phenotypes. Neuroimaging is best thought of as being situated at the interface of the cellular and behavioural/clinical levels. The impact of different genes is widely shared by this stage, thus making the neuroimaging phenotype–genotype mapping a complex many-to-many correspondence problem. Additionally, such mapping parameters are likely to vary with time across life span [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

neuroimaging experiments on low-functioning individuals with ASD have been highlighted by the authors of the review, along with evidence-backed suggestions for overcoming these challenges.

In summary, Jack and Pelphrey have done a significant service to the field as well as the ASD community, by systematically reviewing the empirical literature on three understudied populations within the spectrum. In addition to establishing a clear need for further research on these populations, this review generates crucial questions on the nature of ASD, as well as the most optimal approaches to address them.

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### Correspondence

Bhismadev Chakrabarti, Centre for Autism, School of Psychology and Clinical Language Sciences, University of Reading, Whiteknights, Reading RG6 6AL, UK; Email: [b.chakrabarti@reading.ac.uk](mailto:b.chakrabarti@reading.ac.uk)

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