

Dear Editor,

We would like to submit our article, entitled “Contrastive AI reveals the structure of individual variation in Autism Spectrum Disorder” to be considered for publication in your journal. Autism Spectrum Disorder (ASD) is highly prevalent; extensive research efforts are dedicated to uncovering its biological bases, but this enterprise is complicated by the fact that different individuals with ASD present with large individual differences. Understanding individual differences within ASD is necessary to reveal the causes of the disorder, and to develop more effective, personalized interventions.

In this article, we use state-of-the-art deep learning to isolate individual variation in neuroanatomy specific to ASD, separating it from neuroanatomical variation that is shared with typically developing participants. We show that thanks to this process, previously invisible relationships between neuroanatomy and symptoms become visible: the brains of individuals with ASD correspond to points in a space whose distances correlate with the similarity of their behavior (the results replicate in independent data).

This space lets us address long-standing questions in the field: we find that individual differences between ASD participants are better captured by continuous variation along multiple dimensions (similarly to the approach proposed by the Research Domain Criteria - RDoC), rather than by discrete diagnostic categories. Importantly, these continuous dimensions correspond to changes in localized brain regions, and organize previous results in the literature into a unified framework, also revealing new evidence of alterations in key brain areas for social cognition.

The results are made possible by the interdisciplinary application of contrastive deep learning techniques, combined with a novel analysis approach developed in this study that translates the deep learning results into interpretable insights about the brain. Counterfactual artificial in-

telligence is used to synthesize simulated twin brains matched to individual ASD participants, revealing the impact of the disorder on neuroanatomy.

This manuscript transforms our understanding of Autism Spectrum Disorder. More broadly, it resolves a key challenge that affects the study of all developmental and psychiatric disorders, making available to the research community a new approach to reveal disorder-specific individual differences. For these reasons, the results can be of interest to a very broad readership, including neuroscientists who seek to uncover the biological bases of psychiatric disorders, and clinicians interested in the development of neurally-informed personalized interventions. In light of this, we ask you to consider our manuscript for publication in Science Magazine.

Sincerely,

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