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Categorical Dimensions of Social Impairment and Disrupted Functional Connectivity in Autism Spectrum Disorders: When Does Continuous Become Discrete?

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There is increasing interest in conceptualizing psychiatric impairments from a dimensional rather than categorical perspective, with hope that a new approach will expedite treatment of recalcitrant symptoms that cross diagnostic boundaries and compromise adaptive functioning. The companion paper by Elton *et al.* (1) used a technologically advanced neuroinformatics approach to illustrate that neither a fully dimensional nor fully categorical approach may be adequate. These authors interrogated a developmental disconnection hypothesis of autism spectrum disorder (ASD) (2) through analysis of a large repository of resting-state functional magnetic resonance imaging (fMRI) data, made available through the Autism Brain Imaging Data Exchange (3). Hierarchical linear regression analyses examined disruption in four resting-state networks (dorsal attention, default mode, salience, and executive control) from three perspectives; 1) categorical, contrast of ASD participants with typically developing children; 2) dimensional, an association between functional connectivity and scores on the Social Responsiveness Scale (4) across all participants; and 3) hybrid, test of group differences in the association between the Social Responsiveness Scale and functional connectivity. Although both categorical and dimensional approaches revealed perturbation of resting-state networks, perhaps most interestingly, the hybrid analysis revealed that the strength of these associations between Social Responsiveness Scale and functional connectivity differed between participants with ASD and typically developing children, with discrete areas within each network showing either increased or decreased association strength, depending on group membership. Although some regions showed distinct categorical and dimensional effects, other regions were overlapping, suggesting that the impact of network connectivity on one's social responsiveness may depend partially on whether these networks underwent typical development or were neurodevelopmentally compromised.

From a categorical perspective, there is a longstanding tradition of diagnosing psychopathology within the metaphoric framework of Plato's *Phaedrus*, which stipulates that successful systems theories should "carve nature at its joints." However, the issue of where to make the incision has always been a matter of great debate and subject to

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modification, as reflected by the decision to eliminate Asperger's syndrome as a separate diagnosis in DSM-5. An alternative, dimensional framework has been championed by the Research Domain Criteria (RDoC) initiative as articulated by the National Institute of Mental Health (5). RDoC attempts to describe disorders as products of overlapping dimensional perturbations in genes, molecules, cells, and neural circuits that govern functioning across core domains, including cognitive, negative and positive valence, social perceptual, and arousal and regulatory systems (www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml). By eschewing traditional diagnostic boundaries, RDoC seeks to define disorders from the bottom up by collecting information across different units of analysis and domains with the goal of improving neurobiological validity, clinical prediction, and treatment matching (6). Although these two approaches have been treated as competing models, as suggested by the current study, there is potential value in developing a better understanding of how information gained from these approaches may be integrated to advance our understanding of pathophysiology, treatment, and relationships between comorbid disorders.

Examination of the nosology of ASD and attention-deficit/hyperactivity disorder (ADHD) may help to illustrate this point. Perturbations in social and emotional reciprocity (which coexist with restricted and repetitive interests and behaviors) are a core feature of ASD and, over multiple iterations of the DSM and the ICD, have been a key feature used to differentiate ASD from other neurodevelopmental disorders. Although individuals with ADHD also can demonstrate social dysfunction, this dysfunction often is secondary to challenges created by deficits in attention, impulse control, or both, and typically originates less from impairments in abilities related to social reciprocity, supporting the notion that they are separate diagnostic categories. Conversely, just because these disorders exist within separate categories does not mean that they are orthogonal or that they do not have shared features that could arise from either common or distinct neuropathologic processes. For example, there is growing support for the notion that autism is not a single biological entity, but rather a dimensional disturbance that manifests significant heterogeneity across a wide range of symptoms. Attention deficits and hyperactivity are so common in those with ASD (7) that DSM-5 now permits the two disorders to be diagnosed in the same individuals. Furthermore, as in individuals with ADHD, hypoconnectivity of frontoparietal neural circuits is related to ADHD symptoms in adolescents with ASD (8), suggesting that the two disorders involve a common dysfunction of this underlying neural circuit, a view consistent with the RDoC dimensional perspective. Categorical overlap is also illustrated by a study from our group that found that approximately 20% of those at clinical high risk for psychotic disorders or in a first episode of schizophrenia also met diagnostic criteria for ASD (9). Conversely, children and adolescents with ASD also exhibit elements of thought disorder including illogical thinking and loose associations common to people with schizophrenia (10), suggesting a common impairment in neural circuits involved in language processing across diagnoses. However, as suggested by Elton *et al.* (1), it is also possible that a shared clinical dimension (such as anergia or declarative memory impairment) could result from different pathophysiological mechanisms depending on group membership. Therefore, the final recommendation may be that we strive to avoid reifying diagnostic categories as orthogonal entities, while also not making automatic assumptions that clinical, cognitive, or

functional dimensions necessarily share the same underlying mechanism across all diagnostic groups.

Finally, the companion paper also illustrates an exciting methodologic development in which a neuroinformatics approach is used to ensure reliability and quality assurance of very large functional neuroimaging datasets made possible by the shared contribution of multiple investigators across many research settings. By using this shared data resource, the current study was able to obtain resting-state fMRI data from a larger number of individuals with ASD and typically developing children than normally would be feasible for an individual investigator within a single setting. However, a challenge of many of these shared data repositories is that they often limit their neuroimaging data to structural and resting-state data and often do not include task-based fMRI or other cognitive neuroscience data because of practical concerns about the fidelity of more complicated task-based studies.

Incorporating such task-based studies into these shared data repositories is a worthwhile goal because our ability to ascribe clinical, cognitive, or functional consequences to either increases or decreases in the strength of functional connections within different networks is quite limited if all we have is resting-state data. Elton *et al.* (1) take a step forward by testing the impact that changes in connectivity strength have on social responsiveness, but further progress likely will be facilitated through sharing of task-based fMRI, as was accomplished recently through the Cognitive Neuroscience Test Reliability and Clinical applications for Schizophrenia (CNTRACS) consortium (<http://cntracs.ucdavis.edu/>). For early-onset neurodevelopmental disorders such as ASD, it will also become increasingly critical to create shared databases to examine the development of neural circuits during the 6.5- to 18.7-year period in a fine-grained way that will facilitate understanding of neural maturation during this formative period and will lead to improved treatment outcomes.

In sum, the current study holds out the tantalizing prospect that by continuing the line of inquiry outlined in the study by Elton *et al.* (1), we may one day understand better how other RDoC units of analysis, including genetic and epigenetic effects, modulate the functioning of the neural circuits that underlie various forms of developmental psychopathology. By then examining perturbations in such functioning across various discrete disorders and their shared endophenotypes, we may become closer to making the well-placed incision that will provide insights into nonobvious transdiagnostic intervention and pharmacological and psychosocial treatment strategies to improve mental health.

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