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Neural Connectivity Evidence for a Categorical-Dimensional Hybrid Model of Autism Spectrum Disorder

Amanda Elton, Adriana Di Martino, Heather Cody Hazlett, and Wei Gao

ABSTRACT

BACKGROUND: Autism spectrum disorder (ASD) encompasses a complex manifestation of symptoms that include deficits in social interaction and repetitive or stereotyped interests and behaviors. In keeping with the increasing recognition of the dimensional characteristics of ASD symptoms and the categorical nature of a diagnosis, we sought to delineate the neural mechanisms of ASD symptoms based on the functional connectivity of four known neural networks (i.e., default mode network, dorsal attention network, salience network, and executive control network).

METHODS: We leveraged an open data resource (Autism Brain Imaging Data Exchange) providing resting-state functional magnetic resonance imaging data sets from 90 boys with ASD and 95 typically developing boys. This data set also included the Social Responsiveness Scale as a dimensional measure of ASD traits. Seed-based functional connectivity was paired with linear regression to identify functional connectivity abnormalities associated with categorical effects of ASD diagnosis, dimensional effects of ASD-like behaviors, and their interaction.

RESULTS: Our results revealed the existence of dimensional mechanisms of ASD uniquely affecting each network based on the presence of connectivity-behavioral relationships; these were independent of diagnostic category. However, we also found evidence of categorical differences (i.e., diagnostic group differences) in connectivity strength for each network as well as categorical differences in connectivity-behavioral relationships (i.e., diagnosis-by-behavior interactions), supporting the coexistence of categorical mechanisms of ASD.

CONCLUSIONS: Our findings support a hybrid model for ASD characterization that includes a combination of categorical and dimensional brain mechanisms and provide a novel understanding of the neural underpinnings of ASD.

Keywords: Autism spectrum disorder, Default mode network, Dimensional measures, Functional connectivity, Resting-state fMRI, Social cognition

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Autism spectrum disorder (ASD) is characterized by poor social and reciprocal communication skills combined with repetitive or stereotyped interests and behaviors (1,2). However, a range of symptom severity and functional impairment exists within and across these disorders, in agreement with the notion that ASD represents a spectrum. Previous studies revealed that multiple subtypes of ASD exist along a continuum of the same disorder (3–5). Furthermore, children without a diagnosis of ASD may exhibit varying degrees of social impairment qualitatively similar to ASD without meeting diagnostic criteria, suggesting that the continuum of ASD symptoms may span beyond the categorical diagnosis of ASD (6,7). Therefore, a dimensional characterization of ASD has become increasingly favored within the clinical and research communities, prompting a revision to DSM-5 to include severity ratings for ASD rather than categorical subgroups. In parallel with this clinical evidence, more recent studies have identified dimensional brain-behavior relationships related to ASD (8,9). However, it is unknown whether behaviors observed in children with ASD are similarly represented in the brain as in typically developing children (TDC). Moreover, diagnoses ultimately remain categorical in nature, yet the particular contributions of categorical brain mechanisms, especially after controlling for dimensional relationships, are poorly defined. Studies that systematically examine both the categorical and the dimensional mechanisms of ASD are needed to disentangle the complex neural correlates of ASD.

It has been increasingly recognized that ASD is a disorder of disrupted neural interactions (10). The largest resting-state functional magnetic resonance imaging (fMRI) investigation of ASD to date provided convincing support for this notion (11), as have many other studies (12–17). An examination of functional connectivity measurements represents a promising direction for delineating the potential categorical and dimensional neural mechanisms of ASD. We (18) and others (19) have demonstrated the feasibility of such an endeavor in

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studies of attention-deficit/hyperactivity disorder (ADHD). Specifically, we explored functional connectivity alterations associated with both categorical diagnosis and ADHD symptom severity in relation to four large-scale neural networks: the dorsal attention network (DAN) (20), the default mode network (DMN) (21), the salience network (SAL) (22), and the executive control network (ECN) (23). Findings demonstrated three distinct patterns of brain-behavioral relationships: 1) categorical differences in network-level functional connectivity strength between children with and without a diagnosis of ADHD, supporting the existence of categorically represented neural mechanisms; 2) quantitative relationships between network-level functional connectivity and behavioral measures that were independent of categorical diagnosis, indicating dimensional mechanisms; and 3) diagnostic group differences in the quantitative relationships between network-level functional connectivity and behavioral measures, suggesting qualitatively different behavioral representations in the brain and reinforcing the categorical differences. The demonstration of the presence of three categories of neural mechanisms in ADHD provides a compelling model for studies of other categorically defined disorders that are known to occur along a spectrum; ASD is the next natural candidate given the evidence that ASD symptoms exhibit categorical and dimensional qualities (24). Moreover, the same four networks previously investigated in ADHD are also involved in processes that are disrupted in ASD, including social processing [i.e., DMN (25) and SAL (26)], restricted and repetitive behaviors [i.e., SAL (27)], cognitive control [i.e., ECN and SAL (28)], and attention [i.e., DAN (29)]. A parallel investigation of these networks in ASD to examine the categorical or dimensional nature of this disorder may ultimately aid ASD diagnosis and characterization.

In this study, resting-state fMRI data from 107 TDC and 109 children with ASD selected from a large data repository, the Autism Brain Imaging Data Exchange (11), were analyzed. Functional connectivity measures, derived from four large-scale higher order cognitive networks (i.e., DAN, DMN, SAL, and ECN) were tested to identify three types of effects: 1) categorical differences between TDC and children with ASD in the magnitude of functional connectivity, 2) congruent dimensional relationships between symptom severity and functional connectivity existing across both TDC and children with ASD, and 3) categorical differences between TDC and children with ASD in the relationship between symptom severity and functional connectivity. Our results demonstrate evidence of all three categories of neural mechanisms of ASD.

METHODS AND MATERIALS

Subjects

Data were selected from the Autism Brain Imaging Data Exchange repository of resting-state fMRI scans of children, adolescents, and adults with and without ASD from multiple international sites (http://fcon_1000.projects.nitrc.org/indi/abide/). All sites provided ASD diagnostic status for each subject, and several sites offered various continuous measures of autism-related symptoms. For the present study, sites were selected based on their inclusion of magnetic resonance imaging data, categorical diagnosis, and Social Responsiveness Scale (SRS) scores (30) from TDC and children and adolescents with ASD (age range, 6.5–18.7 years). This limited age range was selected to ensure a similar age distribution across sites and to minimize potential developmental effects of ASD-related neural alterations (31). Because boys are most often affected by this disorder, not enough data sets from girls with ASD were available to draw meaningful estimates of sex effects (32), limiting our analyses to boys. The data sets were further limited to data sets passing the quality assessment protocol performed before release of the preprocessed Autism Brain Imaging Data Exchange data sets to the public. This selection process resulted in 185 subjects, including 95 TDC and 90 children with ASD across four sites (Katholieke Universiteit Leuven [sample 2], New York University, Utah School of Medicine, and Yale University) (Table 1).

The SRS total raw scores, indicating the severity of impairment related to ASD, provided our dimensional measure of ASD. The SRS is a 65-item quantitative assessment based on parent ratings of core deficits pertaining to autism. This assessment offers a continuous measure of ASD as an alternative to other categorically oriented diagnostic tools (30), providing a single score of symptom severity. Children with a categorical diagnosis of ASD and children not meeting ASD diagnostic criteria (TDC) fall somewhere along the continuum of behaviors measured by the SRS.

Table 1. Demographic and Symptom Severity Information of Included Subjects

	All Sites	KU Leuven	NYU	USM	Yale University
Number	185	25	101	25	34
TDC	95	14	51	11	19
ASD	90	11	50	14	15
Autism/Asperger/PDD-NOS	85/17/14	11/0/0	38/8/4	13/0/1	3/4/8
Age (Years)	13.2 (3.2)	14.1 (1.4)	12.0 (3.0)	16.3 (2.4)	12.5 (3.0)
TDC	13.2 (3.1)	14.5 (1.6)	12.5 (3.1)	15.8 (2.6)	12.3 (2.9)
ASD	13.1 (3.3)	13.6 (1.0)	11.5 (2.9)	16.7 (2.2)	12.8 (3.4)
SRS Score	56.4 (43.4)	49.8 (45.0)	57.5 (41.8)	62.0 (46.6)	52.0 (43.1)
TDC	19.1 (14.7)	17.6 (13.6)	22.4 (13.6)	14.6 (12.8)	20.4 (21.3)
ASD	93.0 (28.4)	91.0 (36.0)	91.9 (29.6)	99.3 (22.2)	95.7 (21.1)

Mean (SD) values are provided for each continuous measure.

ASD, autism spectrum disorder; KU Leuven, Katholieke Universiteit Leuven; NYU, New York University; PDD-NOS, pervasive developmental disorder not otherwise specified; SRS, Social Responsiveness Scale; TDC, typically developing children; USM, Utah School of Medicine.