Shared and Distinct Intrinsic Functional Network Centrality in Autism and Attention-Deficit/Hyperactivity Disorder

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Background: Individuals with autism spectrum disorders (ASD) often exhibit symptoms of attention-deficit/hyperactivity disorder (ADHD). Across both disorders, observations of distributed functional abnormalities suggest aberrant large-scale brain network connectivity. Yet, common and distinct network correlates of ASD and ADHD remain unidentified. Here, we aimed to examine patterns of dysconnection in school-age children with ASD and ADHD and typically developing children who completed a resting state functional magnetic resonance imaging scan.

Methods: We measured voxelwise network centrality, functional connectivity metrics indexing local (degree centrality [DC]) and global (eigenvector centrality) functional relationships across the entire brain connectome, in resting state functional magnetic resonance imaging data from 56 children with ASD, 45 children with ADHD, and 50 typically developing children. A one-way analysis of covariance, with group as fixed factor (whole-brain corrected), was followed by post hoc pairwise comparisons.

Results: Cortical and subcortical areas exhibited centrality abnormalities, some common to both ADHD and ASD, such as in precuneus. Others were disorder-specific and included ADHD-related increases in DC in right striatum/pallidum, in contrast with ASD-related increases in bilateral temporolimbic areas. Secondary analyses differentiating children with ASD into those with or without ADHD-like comorbidity (ASD^+ and ASD^-, respectively) revealed that the ASD^+ group shared ADHD-specific abnormalities in basal ganglia. By contrast, centrality increases in temporolimbic areas characterized children with ASD regardless of ADHD-like comorbidity. At the cluster level, eigenvector centrality group patterns were similar to DC.

Conclusions: ADHD and ASD are neurodevelopmental disorders with distinct and overlapping clinical presentations. This work provides evidence for both shared and distinct underlying mechanisms at the large-scale network level.

Key Words: ADHD, amygdala, autism, caudate, functional connectivity, network centrality, precuneus, resting state fMRI

Inattention and hyperactivity/impulsivity, cardinal symptoms of attention-deficit/hyperactivity disorder (ADHD), are frequently reported in individuals with autism spectrum disorders (ASD) (1,2) and are associated with substantial impairment and decreased effectiveness of treatments [e.g., (3)]. Accordingly, clinicians and researchers support elimination of the DSM-IV diagnostic criterion preventing the co-occurring diagnoses of ADHD and ASD. Yet, beyond extensive supportive clinical and epidemiological data (2,4–8), commonalities and distinctions in the neurobiological correlates of ADHD and ASD have been rarely investigated. This is particularly true for neuroimaging (9–11).

Independent examinations of ADHD and ASD increasingly emphasize a role for dysconnectivity in large-scale networks in both disorders [for reviews, see (12–15)], particularly in the default network [e.g., (16–21)] and in fronto-parietal-striatal circuitry [e.g., (17,22–25)]. Given the fundamental distinctions between the prototypic clinical presentations of ASD and ADHD, marked differences in their neural signatures would be expected. Instead, studies directly comparing the neural correlates of ASD and ADHD have found potential commonalities, along with disorder-specific correlates (10,11). A preliminary voxel-based morphometry study comparing children with ASD and ADHD and typically developing control subjects (TDC) (15 per group) revealed common gray matter reductions in medial temporal and left inferior parietal cortex for the clinical groups and ASD-specific reductions in supramarginal gyrus; no ADHD-specific findings were observed (11). Similarly, a recent functional magnetic resonance imaging (fMRI) study directly comparing boys with ASD to those with ADHD and to TDC (20 per group) on a sustained attention task found that both clinical groups exhibited hyperactivation (reduced deactivation) within the precuneus, a default network hub, as well as hypoactivation in areas implicated in attentional control such as superior parietal cortex and striatum. Disorder-specific patterns were also noted, including hypoactivation of dorsolateral prefrontal cortex in ADHD and cerebellar hyperactivation in ASD (10). Although these studies focused on regions rather than circuits, the widely distributed nature of their findings, consistent with the magnetic resonance imaging (MRI) literature for each of the disorders (26–28), further

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supports the notion of dysconnectivity in large-scale networks. Still, the connectivity features underlying ASD and ADHD have not been directly compared (29).

Here, we examined shared and distinct patterns of dysconnectivity in ASD and ADHD. Given the increasing number of circuits implicated in both disorders (13,14), we carried out full-brain exploration of the functional connectome using resting state fMRI data obtained from a substantial sample of children with ASD ($n = 56$) and age-matched and sex-matched children with ADHD ($n = 45$) and TDC ($n = 50$). To achieve this goal, we analyzed voxelwise network centrality. This graph-based measure of network organization captures the functional relationships of a given voxel (node) within the entire connectivity matrix of the brain (connectome), rather than with specific nodes or networks (30–35).

A variety of metrics index network centrality, each emphasizing a different aspect of whole-brain information flow within the connectome (30). We used two commonly employed measures, degree centrality (DC) (30,31,34) and eigenvector centrality (EC) (36). Degree centrality is a local measure of the connectome graph indexing the number of direct connections for a given node. A node has high DC if it has numerous direct connections to other nodes. By contrast, a node has high EC when it is connected with nodes that are highly connected. Eigenvector centrality is a relative global measure that indexes the qualitative superiority of a node's connections, rather than the number of direct connections per se. Accordingly, examining voxelwise DC and EC allowed comparisons between ASD and ADHD of local and global information processing within the functional connectome without requiring selection of a priori nodes or networks of interest.

Finally, despite comorbid ADHD symptomatology in 30% to 60% of children with ASD (2,4–7,37), this overlap is rarely acknowledged in neuroimaging studies, potentially confounding findings. To explore the extent to which ADHD-like comorbidity in ASD shares common neural correlates with ADHD, secondary analyses subdivided the ASD group to compare those with comorbid ADHD symptoms (ASD^+) to those without comorbid ADHD symptoms (ASD^-).

Methods and Materials

Participants

We examined data from 158 children (7.1–13.9 years of age); 7 were excluded for excessive movement. Of the remaining 151 children, 56 children with ASD were group-matched for age, sex, and handedness with 45 children diagnosed with ADHD and 50 TDC, selected from ongoing studies (Table 1). Clinicians' DSM-IV-Text Revision (TR) diagnoses of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified ($n = 39$, $n = 15$, and $n = 2$, respectively) were supported by the Autism Diagnostic Observation Schedule Module 3 (38,39) ($n = 56$; research reliable $n = 53$), review of the child's history, and the Autism Diagnostic Interview-Revised ($n = 54$; research reliable $n = 42$) (40,41). Consistent with previous reports (2,4–7,37), 34 children (61%) with ASD had psychiatric comorbidity based on parent administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (42) ($n = 50$) or unstructured psychiatric interviews ($n = 5$); comorbidity data were missing for one child. Of 34 comorbid children, 28 presented with ADHD (i.e., met DSM-IV-TR criteria except for criterion E) alone or with other Axis I disorders (Table S1 in Supplement 1).

Among children with ADHD, 44 met criteria for combined type ADHD, and 1 met criteria for predominantly inattentive type per K-SADS-PL. Previous studies reported that 20% to 30% of children with ADHD exhibit elevated autistic traits (43,44). To minimize potential confounds, we only included children with ADHD with a parent-based Social Responsiveness Scale (45) inconsistent with autistic traits (i.e., total T-score <65). Seventeen children (38%) with ADHD were diagnosed with comorbid disorders (Table S1 in Supplement 1).

Twenty-nine children (52%) with ASD, 28 children (62%) with ADHD, and all TDC were psychotropic medication-naïve. Details on treatment histories are in Table 1. Current treatment with neuroleptics was exclusionary.

Inclusion as TDC required absence of any DSM-IV-TR Axis I diagnosis. The K-SADS-PL was used for all but one TDC child/parent dyad. Absence of known neurological or genetic syndromes was required for all participants. Intelligence was estimated with the Wechsler Abbreviated Scale of Intelligence (46). Total and verbal IQ, but not performance IQ, were significantly lower in children with ASD relative to TDC. Per the Edinburgh Handedness Inventory (and for one TDC, self-report), 49 TDC, 50 children with ASD, and 44 children with ADHD were right-handed ($\chi^2_2 = 5.2$, $p = .07$). Conners' Parent/Teacher Rating Scales (47) and parent and teacher Social Responsiveness Scales were administered. Per parent-reported ethnicity/race (collected from all but three TDC and one child with ADHD), Hispanic/Latino represented 14%, 21%, and 27% for TDC, ADHD, and ASD, respectively. Groups did not differ significantly in ethnicity/race, age, sex, socioeconomic status, or handedness (Table 1; assessment tools in Supplement 1). All parents and children provided written informed consent/assent, as approved by the New York University (NYU) and the NYU School of Medicine Institutional Review Boards. Data from up to 30 TDC (23,48,49), 17 children with ASD (23), and 18 children with ADHD (50) were included in previous reports.

MRI Data Acquisition

We employed the NYU Center for Brain Imaging Siemens Allegra 3.0 Tesla scanner (Siemens, Iselin, New Jersey). Most children ($n = 127$) completed a 6-minute resting scan comprising 180 contiguous whole-brain functional volumes, acquired using a multiecho echo-planar imaging (EPI) sequence (repetition time = 2000 msec; echo time = 30 msec; flip angle = 90°; 33 slices; matrix = 64 × 64; voxel size = 3 × 3 × 4 mm). Twenty-four children completed a 6-minute 34-second rest scan comprising 197 contiguous volumes, using a single-shot EPI sequence (repetition time = 2000 msec; echo time = 25 msec; flip angle = 90°, 39 slices, matrix = 64 × 64; 3 mm isotropic). Previous studies have demonstrated it is feasible to combine MRI data across sequences (30,48,51–56). To minimize data loss, we obtained two EPI sequences whenever possible. We used the first EPI rest scan for 138 children and the second scan for 13 children who moved excessively during the first scan. Rest scans were collected with eyes open for 132 children, while 19 kept their eyes closed. Groups did not differ significantly on sequence type or scan order, while they marginally differed in eye status (Table 2). We adjusted for these variables and sequence-related variability at group-level analyses. A high-resolution T1-weighted anatomical image was also acquired.

Preprocessing

Consistent with prior work (23,50), data were processed using Analysis of Functional Neuroimages (http://afni.nimh.nih.gov/afni/; Bethesda, Maryland) and the FMRIB Software Library (www.fmrib.ox.ac.uk; Oxford, United Kingdom). Preprocessing comprised slice time correction for interleaved slice acquisition, three-dimensional motion correction, despiking, mean-based intensity