Network Organization Is Globally Atypical in Autism: A Graph Theory Study of Intrinsic Functional Connectivity

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ABSTRACT

BACKGROUND: Despite abundant evidence of brain network anomalies in autism spectrum disorder (ASD), findings have varied from broad functional underconnectivity to broad overconnectivity. Rather than pursuing overly simplifying general hypotheses (i.e., under vs. over), we tested the hypothesis of atypical network distribution in ASD (i.e., the participation of unusual loci in distributed functional networks).

METHODS: We used a selective high-quality data subset from the Autism Brain Imaging Data Exchange (including 111 ASD and 174 typically developing participants) and several graph theory metrics. Resting state functional magnetic resonance imaging data were preprocessed and analyzed for the detection of low-frequency intrinsic signal correlations. Groups were tightly matched for available demographics and head motion.

RESULTS: As hypothesized, the Rand index (reflecting how similar network organization was to a normative set of networks) was significantly lower in participants with ASD compared with typically developing participants. This was accounted for by globally reduced cohesion and density but increased dispersion of networks. While differences in hub architecture did not survive correction, rich club connectivity (among the hubs) was increased in the ASD group.

CONCLUSIONS: Our findings support the model of reduced network integration (i.e., connectivity within networks) and differentiation (or segregation; based on connectivity outside network boundaries) in ASD. While the findings were applied at the global level, they were not equally robust across all networks and in one case (i.e., greater cohesion within ventral attention network in ASD) even reversed.

Keywords: Autism spectrum disorder, Brain networks, Community structure, Graph theory, Intrinsic functional connectivity, Rich club

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Autism spectrum disorder (ASD) is a clinical umbrella term for neurodevelopmental disorders that are characterized by impairments in social behavior and communication skills and by repetitive behaviors and restricted interests. Prevalence estimates have increased rapidly in the last several decades, most recently exceeding 2% (1). Although ASD is generally considered a neurological disorder, findings on brain abnormalities are numerous, with little consensus on what might be crucial or reliable biomarkers. There is, however, some convergence of views implicating aberrant connectivity involving numerous functional networks (2–5). A method of choice in the study of network connectivity has been functional connectivity magnetic resonance imaging (fcMRI), which detects synchronized fluctuations of the blood oxygen level–dependent signal. While the majority of early findings in fcMRI suggested underconnectivity in ASD, growing awareness of methodological (6–8) and maturational issues (9) has resulted in a more complex picture that also includes reports of overconnectivity (10–12), possibly related to impaired network differentiation (13–17).

Given the complexities and inconsistencies of the ASD literature, data-driven techniques provide exploratory approaches that are suitable for uncovering connectivity patterns even in the absence of strong directional hypotheses. Among these, graph theory is particularly suited to comprehensive investigation of whole brain network characteristics (18). Several previous studies using fcMRI and graph theory in ASD have been published (19–26), but some have been limited by small sample sizes (i.e., ≤15 participants in ASD groups) (20,22,24). Rudie *et al.* (23) reported an imbalance between reduced local and increased global efficiency in adolescents with ASD, interpreted as increased randomness of functional network organization. Such apparent randomness, reflected in reduced clustering coefficient and characteristic path length, was also more recently observed in adults with ASD by Itahashi *et al.* (21). Ray *et al.* (26) found atypically increased intrinsic functional connectivity (iFC) inside the "rich club" (i.e., densely interconnected hubs) in ASD, both in a small in-house sample and in a larger low-motion multisite dataset selected from the Autism Brain Imaging Data Exchange (ABIDE) (27).

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ABIDE includes 1112 resting state scans collected at 17 sites. It provides an opportunity for applying strict data quality criteria while maintaining a comparatively large sample size. In the present study, we selected a much smaller (yet sizable) subsample with optimal data quality, in particular minimal head motion, given amply documented confounds in fcMRI from submillimeter movement (28–30). We used graph theory to assess within- and between-network functional connectivity in resting-state functional magnetic resonance imaging (fMRI) scans, using 227 regions of interest (ROIs) from a study establishing function-based nodes for graph theory based on large fMRI samples (31).

Our study differed in several respects from previous graph theory investigations in ASD. Aside from a strong emphasis on quality control and low motion, as described above, we implemented a larger number of ROIs than most previous studies for a comprehensive characterization of network organization in ASD, applying the Rand index (RI), which has not been previously used in ASD. The RI is a measure of similarity between two clustering assignments and can be used for comparison against a normative set of labels (32). In addition, previous studies by Rudie *et al.* (23) and Ray *et al.* (26) used sparsity thresholds or equivalent procedures (22), which reduce sensitivity not only to interindividual differences in noise, but also to global group connectivity differences (e.g., predominant underconnectivity or overconnectivity in ASD). Such predominance of group differences is far from unlikely, and we therefore opted against the sparsity approach, while implementing strict measures to reduce the effects of head motion (described below).

Given the inconsistent findings described above, models proposing general functional underconnectivity (33)—or general overconnectivity—in ASD are probably too simple. However, findings may be compatible with atypical network distribution. Rather than proposing that given networks are either less or more connected in ASD, this hypothesis implies that functionally specialized networks have unusual regional distribution (i.e., these networks include regions that do not participate in the network with corresponding specialization as observed in the typically developing [TD] brain). While some relevant findings have come from studies limited to a single or a few networks of interest (10,14,34–36), the hypothesis of atypical network distribution has received little investigation on a global scale, except for one study reporting increased interindividual variability in a small subsample from ABIDE (37). We hypothesized that in ASD the RI, which is ideally suited as a measure of typicality of network distribution, would be decreased in ASD (because it compares actual against normative network organization). In more specific hypotheses, we expected that cohesion, strength, and density would be reduced, but dispersion increased, reflecting reduced network integration and differentiation (14,16).

METHODS AND MATERIALS

Participants

Data were selected from ABIDE (fcon_1000.projects.nitrc.org/indi/abide/) (27). We emphasized data quality over sample size, because intrinsic fcMRI analyses are exquisitely sensitive to motion artifacts and other noise. Accordingly, we excluded any datasets exhibiting artifacts, signal dropout, suboptimal registration or standardization, or excessive motion (see details below). Sites acquiring fewer than 150 time points were further excluded. These criteria yielded a subsample of 285 participants (174 TD participants and 111 ASD participants ranging in age from 6–36 years). Groups were matched on age, nonverbal IQ, and motion (Table 1; fully detailed participant and site information can be found in Supplemental Table S1).

Table 1. Participant Information

	TD Group	ASD Group	*p* Value
n	174 (16 female)	111 (7 female)	
Age, Years			
Mean (SD)	17.3 (5.8)	17.3 (5.9)	.84
Range	6–35	8–36	
Handedness, *n*			
Left	12	5	
Right	83	51	
Nonverbal IQ			
Mean (SD)	108.6 (11.4)	108.2 (15.3)	.83
Range	67–137	75–149	
Head Motion (RMSD)			
Mean (SD)	0.053 (0.019)	0.054 (0.019)	.82
Range	0.020–0.109	0.018–0.091	

ASD, autism spectrum disorder; L, left; R, right; RMSD, root mean square difference; SD, standard deviation; TD, typically developing.

Handedness data were missing for 79 TD and 55 ASD participants. Nonverbal IQ scores were missing for 14 TD and five ASD participants.

Data Processing

Analysis of Functional NeuroImages (AFNI) (38) (afni.nimh.nih.gov) and FMRIB Software Library (FSL) version 5.0 (39) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) suites were used for data processing. Functional images were slice-time corrected, motion corrected to align to the middle time point, and aligned to the anatomical images using FLIRT with six degrees of freedom. Images were standardized to the Montreal Neurological Institute 152 standard image and resampled to 3-mm isotropic voxels, using FSL's nonlinear registration tool (FNIRT) with sinc interpolation. The outputs were blurred to a global full width at half maximum of 6 mm, using AFNI's 3dBlurToFWHM. Given concerns that traditional filtering approaches can cause rippling of motion confounds to neighboring time points (40), we used a second-order bandpass Butterworth filter (29,41) to isolate low-frequency blood oxygen level–dependent fluctuations (.008 $< f <$ .08 Hz) (42).

To improve data quality, we regressed 17 nuisance variables from the data (29). These included six rigid-body motion parameters derived from motion correction and their first derivatives. FSL's image segmentation (43) was used to create participant-level white matter and ventricular masks, which were trimmed by one voxel to avoid partial-volume effects. An average time series was extracted from each mask and was removed using regression, along with its first derivative. A second-order Butterworth filter (0.008 $< f <$ 0.08 Hz) was used to bandpass all nuisance regressors (29,41,44).

Motion

We quantified motion as framewise displacement (FD) (i.e., the Euclidean distance between consecutive time points [based on