Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 January ; 2(1): 66–75. doi:10.1016/j.bpsc.2016.07.008.

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 (‘under’ vs. ‘over’), we tested the hypothesis of *atypical network distribution* in ASD (i.e., participation of unusual loci in distributed functional networks)

METHODS—We used a selective high-quality data subset from the ABIDE datashare (including 111 ASD and 174 typically developing [TD] participants) and several graph theory metrics. Resting state functional MRI data were preprocessed and analyzed for 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 ASD than TD 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 (connectivity with networks) and differentiation (or segregation; based on connectivity outside network boundaries) in ASD. While the findings applied at the global level, they were not equally robust

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across all networks and in one case (greater cohesion within ventral attention network in ASD) even reversed.

Keywords

Autism Spectrum Disorder; Intrinsic functional connectivity; Brain networks; Graph theory; Community structure; Rich club

Autism spectrum disorder (ASD) is a clinical umbrella term for neurodevelopmental disorders characterized by impairments in social behavior and communication skills, as well as by repetitive behaviors and restricted interests. Prevalence estimates have been rapidly increasing over the 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 MRI (fcMRI), which detects synchronized fluctuations of the blood oxygen-level dependent (BOLD) 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, also including 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 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 (15 in ASD groups) (20, 22, 24). Rudie et al. (23) reported 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 and colleagues (21). Ray and colleagues (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).

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 sub-millimeter movement (28–30). We used graph theory to assess within- and between-network functional connectivity in resting-state 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 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, which has not been previously used in ASD. The Rand index is a measure of similarity between two clustering assignments and can be used for comparison against a normative set of labels (32). Furthermore, 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). Since such predominance of group differences is far from unlikely, we opted against the sparsity approach, while implementing strict measures to reduce effects of head motion (described below).

Given 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., include regions that do not participate in the network with corresponding specialization as observed in the 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 Rand index, 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).

Material and Methods

Participants

Data were selected from ABIDE (fcon_1000.projects.nitrc.org/indi/abide/) (27). We emphasized data quality over sample size, as 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, 111 ASD; ages 6–36 years). Groups were matched on age, nonverbal IQ, and motion (Table 1 for summary and Supplementary Table S1 for fully detailed participant and site information).

Data Processing

Analysis of Functional NeuroImages (AFNI) (38) (afni.nimh.nih.gov) and FMRIB Software library (FSL) 5.0 (39) (fmrib.ox.ac.uk/fsl) 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 MNI152 standard image and resampled to 3mm 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 6mm, 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 band-pass Butterworth filter (41, 42) to isolate low-frequency BOLD fluctuations ($.008 < f < .08$ Hz) (43).

To improve data quality, we regressed 17 nuisance variables from the data (42). These included six rigid-body motion parameters derived from motion correction and their first derivatives. FSL's image segmentation (44) 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 ($.008 < f < .08$ Hz) was used to band-pass all nuisance regressors (41, 42, 45).

Motion

We quantified motion as framewise displacement (FD), i.e., the Euclidean distance between consecutive time points (based on detected six rigid-body motion parameters). For any instance of $FD > 0.25\text{mm}$, the time point as well as the preceding and following time points were censored. When two censored time points occurred within ten time points of each other, all time points between them were also censored. The average number of censored time points per participant did not differ between groups (ASD: 4.9; TD: 4.8; $p = .93$). Datasets were excluded from the analysis if less than 90% of time points or fewer than 150 total time points remained after censoring. Longer runs were truncated to 150 usable time points to reduce variability between datasets. Motion over the truncated run was summarized for each participant as mean FD between time points and was well matched between groups ($p = 0.91$ including all time points, before censoring; $p = .82$ after censoring). The first of these measures (reflecting original motion pre censoring) was also included as a covariate in all analyses to control for any residual motion confounds.

Regions of Interest (ROIs)

We adopted ROIs from a meta-analysis by Power and colleagues (31), which provides a comprehensive set of functionally specialized regions based on a very large number of fMRI datasets. This was considered more suitable than common anatomy-based parcellations given the functional nature of our investigation. Cerebellar ROIs were excluded due to lack of coverage in some datasets, and any ROI missing signal in at least one participant was also excluded. This resulted in 227 ROIs. Mean time series were extracted from each ROI, drawn as 5-mm-radius spheres. Power et al. (31) assigned each ROI to one of eleven networks: auditory, cingulo-opercular task control, default mode, dorsal attention, fronto-parietal task control, memory retrieval, salience, somatosensory/motor (labeled "sensory/somatomotor" in the original study), subcortical, ventral attention, and visual. Since assignments were based on large samples of neurotypical participants, we considered these network assignments as normative for the present study.

Graph Theory

Graph theory is a tool for characterizing networks (46). ROIs, as implemented here, can be considered nodes of a graph, with edges between nodes corresponding to functional connectivity between ROIs. We used the Brain Connectivity Toolbox (46) for calculating graph theoretical metrics, except for Rand Index, which is not available in this toolbox (see below).

The *community structure* of a graph is a clustering of nodes with similar connectivity patterns. Our first objective was to determine the analysis parameters that produced an optimal community structure in the TD group, most closely resembling the normative network organization. To compare with this normative organization, we used the adjusted Rand index (RI), a measure for quantifying how similar two clusterings of nodes are (32). The RI is scaled between 0 (match at chance level) and 1 (perfect match).

We tested three sets of parameters: First, we compared the community structure of data processed with and without global signal regression (GSR), given lack of consensus as to its pros (47) and cons (48, 49). Second, we compared two different algorithms for determining community structure, Newman (50) and Louvain (51). Because the Louvain algorithm can produce different community structures for the same graph, we computed the respective graph measure for each of 100 Louvain-produced community structures and averaged the measure to obtain a summary measure. Last, we investigated thresholding measures using the RI. Most previous studies have used a sparsity approach to thresholding, retaining the top x% of connections in a graph, thus using a fixed number of edges (i.e., connections considered meaningful) in each participant. This approach cancels out any individual differences in strength of connectivity at the global level, which is probably inadequate when implemented in ASD, given previous findings of potentially widespread underconnectivity (3) or overconnectivity (11). Therefore, we used a correlation value threshold (similar to procedures in (52, 53)). In the first case, all positive, weighted edges ($r > 0$) were retained and community structure was computed using the Newman and Louvain algorithms. In the second scenario, all connections—positive and negative—were retained, and community structure of the signed graph was computed using an algorithm developed by Rubinov and Sporns (54), where negative connections oppose nodes belonging to the same community.

After determining optimal parameters for computing community structure in the TD group, we compared the community structure between groups. We used a number of different and in part complementary graph measures to test for group differences in network organization in multiple ways. First, we compared the RI, the number of communities in the community structure, and the *modularity coefficient*, a measure of the degree to which a graph can be subdivided into distinct communities. To investigate additional aspects of community structure, we created three metrics. *Network cohesion* (or correspondence) quantified how well nodes from a normative network grouped within the community structure. For each network, we found the community containing the most nodes from that network and computed what percentage of all network nodes it accounted for. Whole-brain network cohesion was the average across all networks. *Network dispersion* quantified how distributed nodes from a network were in the community structure. For each network, we computed the number of communities containing a node from that network. Whole-brain network

dispersion was the average network dispersion across all networks. Last, *community diversity* described how diverse individual communities were on average. We computed the number of networks appearing in each community and averaged across all communities.

Community structure relies on a balance of strong within-network connectivity, but weaker between-network connections. Consequently, it is important to examine connectivity patterns within and between networks to determine why community structure may differ. We first computed the density and strength separately for all within-network and between-network connections. *Density* is the number of existing connections out of possible connections, treating a connection as binary. *Strength* is the average of all weighted connections between one node and all other nodes and was averaged across all nodes to obtain the average strength for the graph. To examine these measures by individual networks, we computed the density and strength of connections within individual networks, as well as between all possible pairs of networks.

An altered community structure can be indicative of changes in hubs, defined as nodes that connect with a large portion of other nodes, and their connectivity. To identify hubs, we used *betweenness centrality*, which first finds the shortest path between all possible node pairs, and then computes betweenness centrality as how frequently a node participates in these shortest paths. Next, we examined the connectivity structure among hub nodes using the rich-club coefficient (ϕ). To compute the rich-club, we identified hubs using a degree cutoff (k), and then computed the proportion of edges (connections) present between the hubs out of all possible (55, 56). Group-level graphs were obtained by averaging all graphs within each group and retaining only positive connections. We assessed rich-club of our weighted graph over multiple levels, varying the k -level from 50 to 143. Similar to Ray et al. (26), we normalized the rich-club coefficient by the average rich-club from 1000 randomized graphs, $\phi_{norm} = \phi / \phi_{random}$. Rich-club was considered significant for a given k -level if the rich-club coefficient was in the top 5% of the randomized graph coefficients.

Age, motion, and data collection site were used as covariates in all analyses. All graph theoretical measures used weighted graphs except for the implicitly binary density metric.

Results

Rand Index

We first examined effects of analysis parameters on the RI in the TD group to determine which produced an optimal community structure. The highest RI was obtained using GSR, positive-only correlations, and the Louvain algorithm for community detection ($RI=.206$; see illustrative examples of low and high RI in Supplementary Figure S1). This was significantly higher compared to the non-GSR pipeline ($RI=.187$, $p=.002$), inclusion of negative correlations using the Rubinov and Sporns signed community structure algorithm ($RI=.179$, $p<.001$), and Newman's community detection algorithm ($RI=.175$, $p<.001$). Using the optimal parameters (GSR, positive-only, Louvain) to compare between groups, we found the RI significantly reduced in the ASD group ($p=.015$). Groups did not significantly differ, however, on the modularity coefficient ($TD=.333$, $ASD=.333$, $p=.858$) or the number of communities ($TD=3.91$, $ASD=3.99$, $p=.213$).

Network cohesion and dispersion

We next examined network cohesion and dispersion to understand how community structure was altered in ASD compared to TD participants. Whole-brain network cohesion was significantly reduced in ASD ($TD=.707$, $ASD=.684$, $p=.023$). For individual networks, network cohesion was significantly reduced in ASD in the auditory, memory retrieval, somatosensory/motor, and subcortical networks, yet increased in the ventral attention network (Figure 1, Supplementary Table S2). These differences were significant after false discovery rate (FDR) correction (57). Consistently, whole-brain dispersion was significantly increased in ASD globally ($TD=2.76$, $ASD=2.85$, $p=.033$). For individual networks, network dispersion was increased in ASD for the auditory, memory retrieval and subcortical networks (Figure 1, Supplementary Table S2). However, findings for network dispersion did not survive FDR. Last, we found increased community diversity in ASD, although not significantly ($TD=7.85$, $ASD=7.97$, $p=.148$).

Density and strength of connections

Because connectivity patterns determine community structure, we examined the density and strength of network connections to determine the factors driving altered community structure. For all within-network connections, we found a significant decrease in density in ASD ($TD=.092$, $ASD=.090$, $p=.002$) and a marginal reduction in strength ($TD=6.61$, $ASD=6.45$, $p=.058$). At the individual network level, significantly reduced density in the ASD group was found for the auditory and somatosensory/motor networks, with the latter showing reduced strength (all FDR corrected; Figure 1, Supplementary Table S3). Default mode and cingulo-opercular networks showed concordant effects that did not survive FDR correction. Conversely, ventral attention and visual networks had greater mean density and strength in the ASD group, but these differences did not reach significance.

Examining between-network connections, no global group differences in density and strength of between-network connections were found ($p=.659$ and $p=.689$, respectively). However, examining the connectivity between all individual pairs of networks, reduced density and strength in ASD was found for multiple network pairs (Figure 2A–B), but these effects survived FDR correction only for density and strength of connections between auditory and somatosensory/motor networks.

Hub architecture

Finally, we examined betweenness centrality of individual nodes to understand how underlying hub architecture may relate to altered community structure. In both groups, nodes with the highest betweenness centrality were in the salience network (left anterior cingulate cortex). Among the 20 nodes with highest betweenness centrality in the TD group, six fell within the salience, four within the cingulo-opercular task control, four within the default mode, and three within the fronto-parietal task control network (Figure 2C, Supplementary Table S4). We found 14 nodes that differed between groups, ten of which had higher betweenness centrality in the ASD group (Figure 2D, Supplementary Table S5). Three fell in the visual network, two in the fronto-parietal task control network, and one node in each of the somatosensory/motor, default mode, salience, memory retrieval, and dorsal attention networks. Decreased betweenness centrality in the ASD group was seen in

two nodes of the fronto-parietal task control network and one node each in the somatosensory/motor and subcortical networks. However, cautious interpretation of these findings is needed, as a very large overall number of comparisons was performed and the differences described above did not survive FDR correction.

Results for the rich-club analysis showed increased hub interconnectivity with increasing k -level in both groups (Supplementary Figure S2). ϕ_{norm} was significant in the TD group for k between 57 and 143, and in the ASD group between 62 and 143. Comparing groups, the ASD group showed increased rich-club organization for most higher k -levels, consistent with a previous finding (26).

Age and symptom severity

We also explored relations of graph metrics with age and symptom severity. A few negative correlations with age that survived FDR correction were found in the TD group (cohesion for the subcortical network; density and strength for the salience network; strength for memory retrieval network) and in the ASD group (strength in cingulo-opercular task control and dorsal attention networks; Supplementary Table S6). However, no group by age interactions were detected. For betweenness centrality, only 3 nodes (out of 227) in left precuneus (negative correlation), and right precentral and superior medial frontal gyri (positive correlations) showed age-related effects in both groups combined that survived FDR correction (Supplementary Table S7). Again, no group by age interactions were found. There were no correlations between symptom severity measures from ADOS and global density, strength, cohesion, or dispersion (all $p > .05$, uncorr.; Supplementary Table S8). There were also no significant correlations after FDR correction for betweenness centrality and ADOS Total scores for nodes that showed significant group differences in BC (Supplementary Table S5).

Note that any interpretation of these findings requires greatest caution, as these tests were possibly confounded by site differences in age ranges and because ADOS scores were unavailable for 27 out of 111 ASD participants across five sites (Supplementary Table S1).

Discussion

Since neither underconnectivity nor overconnectivity models fully accommodate the highly diverse evidence from the ASD fMRI literature (7, 58), we implemented graph theory metrics to test global and network-specific *atypicality* of network organization, including 285 highest quality ABIDE datasets. We found that functional networks were globally atypical in ASD, with reduced cohesion and increased dispersion, and that connectivity between rich-club nodes was atypically increased.

Network organization in ASD is globally atypical

As hypothesized, a significant reduction in the Rand Index (RI) showed globally atypical network organization in ASD. This finding is consistent with recent reports of “idiosyncratic distortions” in functional connectivity patterns in adults with ASD by Hahamy et al. (37). It is also more broadly consistent with numerous regional findings of atypical functional connectivity in ASD from the rapidly growing fMRI literature (reviewed in 4). As we

applied strict head motion criteria, tightly matched groups for motion, and used motion as covariate in all analyses, our results do not support the proposal that group differences reported in fcMRI studies could be mostly due to uncontrolled motion artifacts (59, 60).

From a developmental perspective, global atypicality (or idiosyncrasy) of network organization in ASD can be traced back to at least two origins that have become well established in recent years. First, although numerous susceptibility genes have been identified for idiopathic ASD (i.e., the non-syndromic type of ASD studied here), an unexpectedly high number of these risk genes have been found to converge functionally onto synaptogenesis, synaptic function, and circuit formation (61–67). A general expectation of network atypicality in ASD is thus reasonable. Second, the huge number of individually variable genetic and epigenetic or environmental risk factors suggests that the clinical umbrella term of ASD may comprise possibly hundreds of different subtypes (68). Given differential etiological pathways, it is fully expected that network organization across individuals fulfilling diagnostic criteria will differ heavily, not only from TD peers, but also within any ASD cohort. One can thus expect *dual divergence*, with respect to both neurotypical development and the ASD population itself, which appears homogeneous only in clinical name, obscuring actual neurobiological heterogeneity. Our finding of network atypicality may capture one facet of this dual divergence in the outcome brain phenotype.

Network cohesion is reduced, but dispersion increased

Neurotypical development is characterized by the activity- and experience-driven emergence of increasingly specialized functional networks (69). These changes are supported by constructive processes (e.g., myelination, synaptic strengthening (70)) and regressive mechanisms (e.g., synaptic pruning, axonal loss (71)), which result in maturational increases in network integration (strengthening connections within the network), but also network differentiation (pruning of connections whose activity levels do not warrant further network participation). Several fMRI studies in TD children are consistent with these principles governing network maturation (72–74). Some recent evidence suggests that seemingly divergent under- and overconnectivity findings in ASD may be reconciled in a model of reductions both in network integration (underconnectivity within neurotypical networks) and in network differentiation or segregation (overconnectivity with atypical regions outside neurotypical networks) (cf. 13, 14–17, 75). Our finding of globally reduced network cohesion combined with increased dispersion in ASD (compared to TD) participants is consistent with this model and suggests that it applies broadly to atypical network organization in ASD, with the possible exception of ventral attention and visual networks. Reduced network integration was further supported by reduced within-network density and (marginally) reduced strength.

The hub architecture is partly altered in ASD and the ‘rich club’ is ‘richer’

Functional hubs, i.e., regions most heavily participating in the shortest connections between all region pairs, were detected using betweenness centrality. The hub metric was highest in regions belonging to the salience, cingulo-opercular and fronto-parietal task control, and default mode networks. This pattern is not surprising, given the known complex interactions between default mode, salience, and task-positive networks (76) and the modulatory impact

of the salience network on DMN and executive control network (77, 78). Studies on the salience network have mostly shown reduced functional connectivity in ASD (for example, (35, 79, 80); but see (81)), possibly suggesting impaired hub function of this network. Yet, no group differences in betweenness centrality surviving multiple comparison correction were found in our study, neither for the salience network nor for others (such as the cingulo-opercular network highlighted in a recent diagnostic prediction study of ASD (82)).

There was, however, a finding for the ‘rich club’ of highly interconnected hubs (56), with increased connectivity in ASD for these nodes, which implement the highest level of communication between networks. While this finding of more densely interconnected hubs in ASD may appear counterintuitive at first, it is consistent with an earlier report by Ray et al. (26), who similar to our study detected functional overconnectivity in ASD for rich club hubs at high k-values, with a concordant finding for structural connectivity from diffusion tensor imaging. Such rich club overconnectivity is likely consistent with findings of reduced network segregation in ASD, first reported by Shih et al. (17) for subregions within posterior superior temporal sulcus, by Rudie et al. (16) for face emotion perception (between amygdala and prefrontal cortex), and then by Rudie et al. (23), who reported globally reduced modularity in ASD. Several more recent studies have generated consistent findings, for somatotopic differentiation (functional segregation) within primary motor cortex (13), and for segregation of DMN (15, 75) and imitation network (14). Seemingly analogous increases in rich club connectivity have also been reported in patients with severe traumatic brain injury (83), suggesting that brain damage or otherwise compromised brain network organization may be accompanied by rich club overconnectivity in some clinical disorders other than ASD (albeit not in ADHD (26)).

Challenges and Limitations

Our finding of globally anomalous network organization in ASD applies at the level of relatively large samples. Although the use of ABIDE data allowed us to select high quality data, the use of multisite data comes at the cost of added factors of variability, including differences in scanners, imaging protocols, resting state instructions, and cohort demographics. However, additional variance in the data must be attributed to true variability within the ASD population, which has been long recognized (e.g., 84). If the clinical umbrella term of ASD comprises “several hundred rare disorders” (68), it is not surprising that the findings reported here will apply not only in different ways across individuals (varying patterns of connectivity anomalies affecting varying sets of networks), but also to different degrees (from severe anomalies to functional connectivity within the normal spectrum). The latter does not imply complete absence of brain network organization in some individuals with ASD, but underscores the importance of multimodal imaging work, examining connectivity with combined anatomical and functional assays, including temporal dynamics that can be best detected by electrophysiological techniques. Unfortunately, rich multimodal studies of neurofunctional organization in ASD remain scarce to date and use of large-sample ABIDE data limited the present study to the resting state fMRI technique.

We selected a set of ROIs based on function (rather than anatomy), but these ROIs were derived from studies in adults, whereas our study also included children and adolescents.

This may explain why the RI for the TD group – although significantly higher than in the ASD group – remained itself moderate. The inclusionary age range in our study was also wide (6–36 years). Although we included age as nuisance covariate, maturational changes may have affected the graph metrics tested here. In addition, our ASD sample did not represent the full spectrum of autistic disorders, due to the need for almost completely motion-free data in fcMRI, which can usually only be acquired from high-functioning participants. Little evidence from fMRI exists for low functioning children with ASD, and our findings could not help fill this gap.

Conclusions

Using graph theory for a comprehensive global and network-specific examination of intrinsic functional connectivity, we found broad evidence of atypical network organization in children and young adults with ASD. Reduced network cohesion and increased dispersion and rich club connectivity in ASD are compatible with a developmental model of impaired network integration and differentiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health (grant R01-MH081023), with additional funding from NIH/NIGMS IMSD 5R25GM058906-13 (author JOM). All authors report no biomedical financial interests or potential conflicts of interest.

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Figure 1.

For each network, bar plot indicates levels for cohesion, dispersion, density, and strength in the TD (blue) and the ASD group (red). * $p < .05$ (FDR corrected), † $p < .05$ (uncorr.).

Figure 2.

Density (A) and strength (B) for connectivity between each network pair. Group averages are shown for the TD group in the lower-left triangle and for the ASD group in the upper-right triangle. Network connections with lower density or strength are denoted by dashes (bold indicating $p < .05$ after FDR correction). Approximate location of (C) nodes with highest betweenness centrality in the TD group (yellow), and (D) nodes with greater (red) or reduced (blue) betweenness centrality in ASD (all $p < .05$, uncorrected).

Table 1

Participant information

	TD group	ASD group	p-value
n	174 (16 female)	111 (7 female)	
Age (years)	17.3 (5.8) 6–35	17.3 (5.9) 8–36	0.84
Handedness	12 L, 83 R	5 L, 51 R	
Non-Verbal IQ	108.6 (11.4) 67–137	108.2 (15.3) 75–149	0.83
Head motion (RMSD)	0.053 (.019) .020–.109	0.054 (.019) .018–.091	0.82

RMSD, root-mean-square difference; handedness missing for 79 TD and 55 ASD; nonverbal IQ scores were missing for fourteen TD and five ASD subjects.