Altered global modular organization of intrinsic functional connectivity in autism arises from atypical node-level processing

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Abstract
Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by restricted interests and repetitive behaviors as well as social-communication deficits. These traits are associated with atypicality of functional brain networks. Modular organization in the brain plays a crucial role in network stability and adaptability for neurodevelopment. Previous neuroimaging research demonstrates discrepancies in studies of functional brain modular organization in ASD. These discrepancies result from the examination of mixed age groups. Furthermore, recent findings suggest that while much attention has been given to deriving atlases and measuring the connections between nodes, within node information may also be crucial in determining altered modular organization in ASD compared with typical development (TD). However, altered modular organization originating from systematic nodal changes are yet to be explored in younger children with ASD. Here, we used graph-theoretical measures to fill this knowledge gap. To this end, we utilized multicenter resting-state fMRI data collected from 5 to 10-year-old children—34 ASD and 40 TD obtained from the Autism Brain Image Data Exchange (ABIDE) I and II. We demonstrate that alterations in topological roles and modular cohesiveness are the two key properties of brain regions anchored in default mode, sensorimotor, and salience networks, and primarily relate to social and sensory deficits in children with ASD. These results demonstrate that atypical global network organization in children with ASD arises from nodal role changes, and contribute to the growing body of literature suggesting that there is interesting information within nodes providing critical markers of functional brain networks in autistic children.

Lay Summary
Modular organization in the brain plays a crucial role in network stability and adaptability for neurodevelopment. Altered global modularity demonstrates discrepancies in prior studies of functional brain modular organization in autism spectrum disorder (ASD). These discrepancies result from the examination of mixed age groups. In the present study, we examined how such discrepancies and altered global modular organization in ASD originates from atypicality at the systematic nodal level, focusing on children with ASD. We demonstrate that many of the previous discrepancies of altered functional connectivity in ASD could be reconciled based on nodal role identification and functional cartography of nodes. Our findings suggest that alterations in nodal topology may start occurring at early ages in children with ASD.

KEYWORDS
ABIDE, autism spectrum disorder, graph-theory, modular organization, nodal cartography, normalized mutual information, resting-state functional connectivity

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INTRODUCTION

Graph-theoretical approaches applied to magnetic resonance imaging (MRI) data have revealed that the human brain exhibits a hierarchical modular organization, with relatively larger functional communities further divisible into smaller communities (Meunier et al., 2010; Sporns & Betzel, 2016). Within these modular partitions, each brain region (node) has its distinct functional role in information processing within and across different modules, determined by a specific profile of within- and between module connectivity. This modular profile of nodes helps classify them into different node types, whose relative properties may affect information flow within a complex network system (Sporns, 2014). Identification of functional brain modular structures can be used to delineate functional components associated with specific biological functions (Hsu et al., 2012). Modular structures play a crucial role in network stability and adaptability to facilitate optimal network functioning (Bassett & Gazzaniga, 2011; Bullmore & Bassett, 2011; He et al., 2009). The modular organization of the brain may play a crucial role in evolution and neurodevelopment (Meunier et al., 2009).

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by restricted interests and repetitive behaviors as well as difficulty with social-communication skills. Recent studies on static functional connectivity (SFC) analysis of resting-state functional magnetic resonance imaging (rsfMRI) data have shown atypical functional connectivity and functional brain network configurations associated with social cognitive abilities in individuals with ASD (Chen et al., 2018; Hull et al., 2017; Li et al., 2021). These findings are in broad agreement with the previous literature reporting atypical functional connectivity and functional brain network configurations associated with social cognitive abilities in individuals with ASD (Rudie et al., 2012, 2013). Previous resting-state and task fMRI studies have also suggested links between cognitive functions and modular organization of functional brain networks. Associations have been observed between cognitive abilities (e.g., intelligence, working memory performance, social and emotional processing) and (a) modular network organization (Cohen & D’Esposito, 2016; Hilger et al., 2017; Hilger et al., 2020; Stevens et al., 2012), (b) proportions of specific node types (i.e., connector hubs and provincial hubs) and (c) alteration in topological roles of brain regions (Cohen & D’Esposito, 2016; Hilger et al., 2020; Hilger et al., 2017; Stanley et al., 2014). Glerean and colleagues (Glerean et al., 2016) reported group differences (age 19–47 years) in the composition of the default mode network (DMN) and a ventral-temporal-limbic (VTL) subnetwork (amygdala, striatum, thalamus, parahippocampal gyrus (PhG), fusiform gyrus (FuG), and inferior frontal gyrus). These findings were significantly correlated with autism symptom severity scores. These studies suggest that individual differences in the modular organization and the topological roles of the nodes of functional brain networks are related to behavioral traits in ASD.

Previous studies explored large-scale and region-specific modular properties, which included subjects with a wide range of ages, stratifying individuals into different age cohorts (e.g., mixed children and adolescents [4–17 years]), resulting in mixed findings throughout the autism neuroimaging literature (Nomi & Uddin, 2015; Uddin et al., 2013). Between the age range of 5–10, hubs shift from being localized in motor areas and primary sensory areas to a more distributed pattern across frontal, temporal, visual, and subcortical regions (Supekar et al., 2009). This shift of hubs reflects the development of higher order cognition during this period (Oldham & Fornito, 2019). However, atypicality in large-scale and regional modular properties in younger children with ASD remains unexplored. Here, we address fundamental questions about the influence of alteration in topological roles of brain regions on global modular properties of the brain in younger children with ASD (5–10 years). An outstanding question is (a) whether alteration of global modular structure arises from the atypical modular cohesiveness of specific brain regions in children with ASD, and (b) whether alteration in the topological roles of specific brain regions is responsible for atypical modular configuration and FC in children with ASD.

In this study, we applied a graph-theoretical approach to resting-state fMRI data from a sample of high-functioning children with ASD and typically developing (TD) children available through the Autism Brain Imaging Exchange (ABIDE) (Di Martino et al., 2014, 2017). We included children between 5 and 10 years of age who were male, right-handed, and had full-scale IQ > 75 from multiple datasets to test for between-group differences in the modular configuration of sensory-motor and neurocognitive networks between ASD and TD children and links to autism symptom severity.

METHODS

Participants

We used resting-state fMRI data collected from children with ASD (5–10 years; males; right-handed; IQ > 75) from all ABIDE I & II sites (New York University, Stanford University, San Diego State University) (Di Martino et al., 2014, 2017) that had participants in the age range 5–10. Each of the contributing sites confirmed diagnosis of ASD through a combination of clinical judgment and/or standard diagnostic instruments (Autism Diagnostic Observation Schedule (ADOS) and/or Autism Diagnostic Interview (ADI)) (Table 1).

We excluded subjects based on the following criteria: (1) high levels of head motion (maximum motion ≥2 mm or 2°rotation, or more than 50% of frames with high
framewise displacement (FD); time points with FD was larger than 0.5 mm, along with the preceding time-point and following two time-points, were defined as high head motion time points); (2) incomplete cortical coverage in the scan; (3) age above 3 SD/C6 mean across the samples; (4) full intelligence quotient (verbal + non-verbal) (FIQ) above 2SD/C6 mean across the samples; (5) sites with less than 10 subjects.

Data selection and preprocessing

Resting-state fMRI data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox (http://rfmri.org/DPARSF) (Chao-Gan & Yu-Feng, 2010). The initial 10 volumes were dropped to ensure steady-state longitudinal magnetization. The functional images were realigned using a six-parameter (rigid body) linear transformation. Structural images (T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE)) were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and co-registered to the mean functional images using a 6 degree of freedom linear transformation. Subsequently, structural images were transformed into standard Montreal Neurological Institute (MNI) space at the resolution of 3 mm^3 isotropic voxels using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) tool (Ashburner, 2007). The following nuisance signals were removed: head motion effects (Friston 24-parameters) (Friston et al., 1995), signals from WM and CSF, and linear and quadratic trends. WM and CSF signals were regressed using an anatomical component-based noise correction procedure (aCompCor) (Behzadi et al., 2007). We did not use global signal regression (GSR) since it has been shown to influence anti-correlations in resting-state brain networks and distort group differences in intrinsic functional connectivity (Murphy et al., 2009; Weissenbacher et al., 2009). Finally, a temporal bandpass filter (0.01–0.1 Hz) was applied to the blood oxygen level dependent signals measured in MRI (BOLD) time series (Liu & Duyn, 2013). All normalized images were smoothed with a Gaussian kernel to 6 mm full-width at half-maximum (FWHM). Given that head motion-based artifacts influence BOLD signals (Power et al., 2014), we performed covariate regressions of Friston 24-motion parameters using the DPARSF toolbox. To further minimize the impact of head motion artifacts, the scrubbing method was applied, wherein, frames/scans with framewise displacement (FD) >0.5 mm were discarded (flagged frame as well as one before and two after) (Power et al., 2012). The maximum number of time points scrubbed with FD >0.5 mm for any individual was 4 (0.08%/C6 0.04%) in the ASD group and 3 (0.06%/C6 0.04%) in the TD group.

Construction of resting-state functional connectivity matrix

Graph properties such as modularity are strongly influenced by different graph densities (Ginestet et al., 2011). We thresholded our correlation matrix over a range of thresholds, retaining the strongest 15, 20, 25, 30, 35, 40, and 45% edges. This resulted in seven thresholded graphs for each subject (see Supplementary methods). To parcelate the brain into regions of interest (ROIs), we used the Schaefer-Yeo 2018 atlas with 200 parcellations (Schaefer et al., 2018) (see Supp. methods for parcellations 400 and 600). We used the DPARSF toolbox to extract the BOLD time series of each brain region and to construct a subject-specific N x N connectivity matrix, which contains the FC between each pair of nodes. Functional

| TABLE 1 Participants demographics | ASD (n = 34) | TD (n = 40) | Group comparisons (p-value) |
|----------------------------------|-------------|-------------|-----------------------------|
| Age (years)                      | 9.36 ± 1.74 | 9.67 ± 1.54 | 0.31^a                      |
| Site × group interaction         |             |             | 0.25^b                      |
| Full-scale IQ (C6)               | 110.43 ± 16.83 | 114.46 ± 13.42 | 0.21^a                      |
| Site × group interaction         |             |             | 0.74^b                      |
| Mean FD (mm)                     | 0.14 ± 0.04 | 0.12 ± 0.04  | 0.11^a                      |
| Site × group interaction         |             |             | 0.32^b                      |
| ADOS score                       |             |             |                             |
| Total score                      | 12.15 ± 4.21 |             |                             |
| Social                           | 9.36 ± 3.44 |             |                             |
| RRB score                        | 2.78 ± 1.70 |             |                             |
| Severity score                   | 7.01 ± 1.77 |             |                             |

Abbreviations: ADOS, autism diagnostic observation schedule; RRB, restricted and repetitive behaviors. FD, framewise displacement.
^aTwo-sample t-test.
^bANOVA.
connectivity between brain regions was estimated by calculating Pearson’s correlation coefficient values of the BOLD signal between the BOLD time series. These values were then normalized to z-values using Fisher’s z transformation.

Graph-theoretical analysis

Modular organization measures

We used three community detection algorithm to assess the reliability of our findings across different methods—Louvain (Blondel et al., 2008), Newman-Girvan (Newman & Girvan, 2004), and consensus agreement (Lancichinetti & Fortunato, 2012). These algorithms were applied separately on the seven thresholded graphs and the resulting graph metrics were averaged for each participant.

We explored three whole-brain measures of the functional network modular organization for each subject: global modularity $Q$, number of modules, and module size. Global modularity $Q$-values represent the proportion of within-module edges in the network minus expected within-module edges calculated from a similar random network (Newman, 2006). Global modularity value $Q > 0.3$ indicates a modular network structure. The Louvain method and consensus agreement method showed similar results; however, the Louvain method provided consistent results across all the participants for all three modularity measures. Thus, the Louvain method was used for further analyses. We performed 100 optimization runs on each subject. Statistical analysis on subject-specific values (obtained by averaging across results of all the threshold-defined graphs) for these whole-brain modularity measures was conducted using permutation testing (10,000 iterations, $p < 0.05$, false-positive discovery rate correction (FDR) corrected).

Modular composition analyses

Group-level modularity composition analyses

The modularity measures can only reflect differences in network modularity; these measures cannot reveal differences in modular composition between groups. Normalized mutual information (NMI) metrics (Kuncheva & Hadjitodorov, 2004) were used to compute group-level similarity in the whole-brain community structure between groups using NMI function in the Brain Connectivity toolbox (Rubinov & Sporns, 2010). This tool computes an NMI-based similarity value, ranging from zero to one, wherein a similarity value closer to one represents identical community affiliation/assignment (see Supplementary methods).

Subject-level modularity composition analyses

When partitions are compared across two subjects, even if two modules might appear quite similar, they may not have the same labels. In other words, a community detection algorithm might assign different labels to different modules across subjects. This problem can be solved either by manual intervention or by overlapping modules with the same label while preserving the differences in modular partitions between groups. Using the NMI approach, we can study the difference in community structure within and between groups at the individual subject-level and node-level (see Supplementary methods).

Within- and between-module connectivity metrics

An altered community structure can be indicative of changes in the integration and segregation of functional networks, which can be explored by uncovering the intra- and inter-module connectivity patterns of individual nodes. The two measures proposed by Guimerà and Amaral (2005)—participation coefficient (pc) and within-module degree ($z$)—were used to characterize the connectivity of nodes within and between modules. The participation coefficient is defined as the distribution of a node’s edges among the modules/communities of a graph. The participation coefficient of a node ranges from 0 to 1, where 0 denotes that all its edges are within its own community and 1 denotes the uniform distribution of its edges across its own and other modules. Within-module degree shows how well a node is connected to other nodes in its own community. Positive values represent high connectivity of a node to nodes within its own community, whereas negative values represent low connectivity within the same community. These two-graph metrics were calculated for binarized and proportionally thresholded graphs using seven different cut-offs (15%, 20%, 25%, 30%, 35%, 40%, or 45% strongest edges). For each participant, graph metrics were averaged across these six thresholds to generate individual mean maps. For visualization purposes, individual mean pc- and z-values of each node were averaged across participants. A two-sample t-test was used to compare these graph metrics between groups, followed by FDR correction.

Node-type cartographic categorization

Guimerà and Amaral (2005) classified nodes into seven hubs and non-hubs based on their within- and between module connectivity profiles. Hubs were classified as Provincial (PHUB) (strong within module connectivity, weak between module connectivity), Connector (CHUB) (strong between-network, weak within-network connectivity), and Kinless (KHUB) (equal within- and between-
module connectivity). In contrast, non-hubs were classified as ultra-peripheral (strongest within module connectivity), Peripheral (contains most connections within the same module), Nonhub connectors (many links with nodes in other modules), Nonhub kinless (most links with nodes in other modules). We classified nodes as hubs and non-hubs based on within-module degree values, $z \geq 1$ as hubs, and $z < 1$ as non-hubs. Non-hubs were further classified into subtypes based on participation coefficient values, ultra-peripheral (pc $\leq 0.05$), peripheral (0.05 $\leq$ pc $\leq 0.62$), non-hub connector (0.62 $<$ pc $\leq 0.80$), and non-hub kinless nodes (pc $>0.80$), whereas hubs were divided into three subtypes—provincial (pc $\leq 0.30$), connector (0.30 $<$ pc $\leq 0.75$), or kinless hubs (pc $>0.75$). Proportions of node types were also calculated for binarized and proportionally thresholded graphs using six different cutoffs. For each participant, the proportion of each node type was calculated by averaging across the six thresholds. For visualization purposes, individual node-type proportions were averaged across all the subjects to generate group averaged proportions of node types. A two-sample Mann–Whitney $U$ test was used to compare these graph metrics between groups, followed by FDR correction.

Node-role identification

To identify a specific global role of each brain region, the participation coefficient (pc) and within-module degree (z) of each node were categorized as a subtype of hub/non-hub for each subject, and a node was regarded as a specific hub/non-non-hub based on its average frequency of occurrence in a group (i.e., the frequency of occurrence should be more than 50% of the subjects in the group). These measures were calculated for binarized and seven proportionally thresholded graphs.

### RESULTS

**Global modular organization and ASD symptoms**

We first examined three global modularity measures of brain networks using the Louvain algorithm (see Supplementary table 1 for Newman and Consensus agreement community detection results). The ASD group showed significantly reduced global modularity Q compared with the TD group ($p = 0.001$). We also observed a significant increase in the average number of modules ($p = 0.02$) and a significant decrease in the average modular size in the ASD group ($p = 0.01$) (Table 2, Figure 1). None of the whole-brain global measures of the modular organization were significantly associated with Autism Diagnostic Observation schedule (ADOS) scores (Table 3).

**Reduced similarity in modular composition in the ASD group**

**Group-level analyses**

A qualitative examination of group average modular structures (Figure 2) revealed that overall network structure and FC were well preserved in both groups.

### TABLE 2 Group differences in global modularity measures

|                        | ASD mean (± std) | TD mean (± std) | $p$-value |
|------------------------|-----------------|----------------|----------|
| Whole-brain global modularity measures |                  |                |          |
| Global modularity       | 0.28 (±0.04)    | 0.30 (±0.03)   | 0.001    |
| Average number of modules | 2.99 (±0.52) | 2.81 (±0.39)  | 0.02     |
| Average module size     | 72.89 (±13.42)  | 78.57 (±13.82) | 0.01     |
| Whole-brain proportion of node types |                  |                |          |
| Connector hubs          | 11.54 (±2.58)   | 10.77 (±2.92)  | 0.12     |
| Provincial hubs         | 3.46 (±2.45)    | 4.43 (±2.63)   | 0.02     |
| Kinless hubs            | 0.019 (±0.05)   | 0.003 (±0.01)  | 0.02     |
| Nonhub connector nodes  | 19.09 (±10.34)  | 14.97 (±8.04)  | 0.008    |
| Peripheral nodes        | 62.48 (±10.14)  | 66.59 (±7.73)  | 0.007    |
| Nonhub Kinless nodes    | 0.002 (±0.016)  | 0.001 (±0.007) | 0.65     |
| Ultra-peripheral nodes  | 3.40 (±2.62)    | 3.24 (±2.31)   | 0.65     |

*Note: The group difference for global modularity measures was calculated using permutation test (10,000 iterations, $p < 0.05$) whereas whole-brain proportion of node types was calculated using Mann–Whitney $U$ test.*
Quantitative examination of the similarity between mean ASD and TD network structures (Table 4) using NMI also showed a high level of similarity of network structures (averaged across proportional thresholds, mean NMI = 0.66, standard deviation = 0.13). For each participant, these global measures were calculated by averaging across all the thresholds and for each group, these measures were averaged across all the subjects. The Louvain and consensus agreement community-detection methods produced similar results as compared to Newman-Girvan methods (b & c).

Subject-level analyses

Individual subject network partitions revealed that the mean NMI of all within-group subject pairs was significantly higher than the mean of all between-group subject pairs for all the thresholds except for one (Table 5). Additionally, across all the thresholds, the average within-group NMI for the ASD group was less than the average-within TD group NMI, reflecting the heterogeneity of network partitions in the ASD group (see Supplementary Tables 3 and 4 for group differences in modular composition across two atlas parcellations).

Node-level analyses

To further investigate the brain regions responsible for the significant group difference in modular structure, we used permutation tests of community assignments...
First, the significant nodes were selected using FDR corrected $p < 0.05$ as a significance criterion, and the percent of significant nodes within each network was counted. Figure 3a shows that there was an inconsistency in community assignments in the ASD group with a high percentage of ROIs in the sensorimotor (SM) networks across all the threshold densities. Additionally, this community membership variability across groups was also contributed to by a smaller percentage of nodes in DMN, visual, salience (Sal), and central executive network (CEN). To further illustrate

FIGURE 2  Group-level difference in the community structure revealed overall similarity between ASD and TD groups. (a). The networks are on the vertical axis and graph densities are on the horizontal axis. Regions are colored by the community assignments of the ROIs. (b). The community structure of ASD group at the 20% graph density. (c). The community structure of TD group at the 20% graph density. The group-level community structures were detected using group-averaged functional connectivity matrices. The 20% graph density was used as representative community structure over a range of thresholds on the basis NMI.

TABLE 4  NMI values between ASD and TD (supplementary)

| Proportional threshold | TD X ASD |
|------------------------|----------|
| 15%                    | 0.78     |
| 20%                    | 0.58     |
| 25%                    | 0.62     |
| 30%                    | 0.90     |
| 35%                    | 0.50     |
| 40%                    | 0.61     |
| 45%                    | 0.63     |
| Mean across proportional threshold | 0.66     |
| Standard deviation     | 0.13     |

Note: Group-level community structure similarity between ASD and TD across all the thresholds.

(Alexander-Bloch et al., 2012). First, the significant nodes were selected using FDR corrected $p < 0.05$ as a significance criterion, and the percent of significant nodes within each network was counted. Figure 3a shows that there was an inconsistency in community assignments in the ASD group with a high percentage of ROIs in the sensorimotor (SM) networks across all the threshold densities. Additionally, this community membership variability across groups was also contributed to by a smaller percentage of nodes in DMN, visual, salience (Sal), and central executive network (CEN). To further illustrate

the nodes contributing to the differences in the community structure and NMI between ASD and TD, the ROIs with significantly inconsistent/flexible community membership (FDR corrected, $p < 0.05$) across all the threshold densities are represented on the brain (Figure 3b). The difference in the diagnostic network structures are driven by 38% of the nodes. Most notable community membership discrepancies were contributed by lateral occipital cortex (LoCc), precentral gyrus (PrG), postcentral gyrus (PoG), superior temporal gyrus (STG), dorso-medial prefrontal cortex (dmPFC), precuneus (Pcun), inferior parietal lobule (IPL), and lateral prefrontal cortex (lPFC).

Association with ASD symptoms

The community assignment consistency values (Pearson’s phi coefficient) of the majority of inconsistent nodes (dmPFC, Pcun, LocC, medial ventral occipital cortex (MvocC), IPFC, cingulate gyrus (CG)) were negatively associated with ADOS-social, total and severity scores whereas these community assignment consistency values of nodes such as (dmPFC, PoG, IPFC, LocC, MvocC) were also negatively associated with restricted and repetitive behavior (RRB) scores. These results suggest that with increasing symptom severity the tendency of nodes
to switch modules within the ASD group also increases (i.e., reduced stability of nodes within their respective modules).

### Altered modular connectivity

To investigate group differences in modular connectivity, we used two measures: participation coefficient PC (inter-modular connectivity) and within-module degree Z (intra-modular connectivity). In ASD, a significantly (FDR corrected, \( p < 0.01 \)) increased participation coefficient was observed for nodes in bilateral PCun, bilateral PrG, and PoG, rIPL, and rPCun (Table 6, Figure 4a, b). The nodes with significant differences in within-module degree did not survive FDR correction, however, in ASD significant (all \( p < 0.05 \)) increase in intramodular connectivity was contributed to by nodes of bilateral LoCe, bilateral temporal lobe, and left (medial orbito-frontal gyrus) mOFG. A significant decrease in within-module connectivity was observed in nodes of right IFG and SFG, bilateral paracentral lobules (PCL), bilateral PoG, rIPL and frontal eye field (FEF), and left lingual cortex and right cuneus cortex consisting of the MvocC node (Table 6, Figure 4c, d). The within-module connectivity values of bilateral nodes of dmPFC were negatively \( (r = -0.3, p = 0.01) \) associated with the ADOS RRB score whereas the between-module connectivity of the same nodes was positively correlated \( (r = 0.3, p = 0.02) \) with ADOS severity scores. The average participation coefficient scores of DMN, Sal, and SM networks were also negatively correlated with global modularity.
(r = −0.58, p < 0.0001) thus further suggesting that the increased between-module connectivity in ASD results in less robust modular organization contributed by nodes of these networks. Furthermore, in the ASD group, there was a strong negative correlation between the PC with community assignment consistency scores of the nodes with increased flexibility (which switched their modules across different subjects) (Figure 4e, f) (see Supplementary Figure 1 for group-differences in modular connectivity across two atlas parcellations).

### Functional cartography reveals significant differences in node types in the ASD group

The topological roles of ROIs in facilitating within and between module communication were characterized using PC and within-module degree Z. Figure 5b shows that only 15.18% of nodes were characterized as hubs (i.e., kinless, connector, or provincial hubs) and the majority of the node types were peripheral and non-hub connectors. In ASD, proportions of peripheral and provincial nodes were significantly reduced, whereas proportions of non-hub connector nodes and connector hubs were significantly increased (Table 2). However, the proportion of node types showed no significant association with ADOS scores (Table 3) (see Supplementary Figure 3 for group-differences in modular composition across two atlas parcellations).

### Nodal-role identification

We further examined brain regions which contributed to the altered proportions of the node types. Examination of the group average matrix shows that the majority of peripheral nodes in TD converted to non-hub connectors (PrG, PoG, IPFC, PCun, ventral PFC, and insula) and few peripheral nodes to connector hubs in ASD (bilateral dmPFC, IPFC, right PoG). The provincial nodes in TD switched their roles to connector nodes in ASD (like the left IPL from DMN (Figure 6a, b)). Subject-level analyses revealed that the ASD group had 19 non-hub connector nodes and five connector hubs compared with the TD group with four non-hub connector nodes and two connector nodes (Figure 6e–g, Tables 7 and 8). Common non-hub connectors (eight nodes) were from the left LoCc, left FuG, bilateral PCL, and rOFC. Additionally,
FIGURE 4  Legend on next page.
the ASD group had 13 non-hub connectors from the bilateral temporal pole and FEF, left OFC and right medial temporal lobe, and bilateral vPFC. Common connector hubs were from bilateral STG, bilateral Insula cortex, and right dmPFC. The ASD group had five connector hubs from bilateral STG, bilateral posterior cingulate cortex (PCC), and left FuG, whereas the TD group had two extra connectors from the dmPFC.

The majority of non-hub connector nodes in the ASD group had increased between-module connectivity (FDR uncorrected, all $p < 0.05$), reflecting the influence of these nodes as non-hub connectors on increased inter-module connectivity in ASD populations (Figure 6c). Similarly, connector hubs (left FuG and rPCC) in ASD had increased inter-modular connectivity (FDR uncorrected, all $p < 0.05$).

**DISCUSSION**

Autism spectrum disorder is a ‘critical period’ neurodevelopmental disorder associated with atypical development of brain networks. Neurobiological research suggests that autism arises from aberrant maturation processes of brain development during critical periods of plasticity. Atypical functional connectivity and poorly connected functional brain networks may arise from the increased ratio of excitation/inhibition resulting in hyperexcitability and thus cortical instability in ASD (Rubenstein & Merzenich, 2003). Furthermore, these functional brain network atypicalities in ASD may also be associated with synaptic cell-adhesion molecules and altered expressions of genes encoding these molecules, which play important roles in synaptic-formation and axonal guidance (Arons et al., 2012; Földy et al., 2013; Jamain et al., 2003; Redies et al., 2012). Most of the neuroimaging studies examining brain network organization in ASD have focused on older children, adolescents, and adults, with less work on younger children (5–10 years), thereby resulting in discrepancies in the atypicality of FC and networks reported in individuals with ASD (Bernhardt et al., 2017; Hernandez et al., 2014). In our study, we systematically investigated global and regional module properties related to atypical cognitive skills and social communication deficits in younger children with ASD. The results demonstrated that, at the nodal level, reduction in modular composition and alteration of modular connectivity in the ASD group was significantly associated with ADOS scores, while whole-brain global measures of modular organization and proportion of nodal types showed no significant association with ADOS scores.

We used graph-theoretical analysis applied to resting-state fMRI data from ABIDE. We report evidence for...
FIGURE 6  Group-differences in topological roles of nodes. (a) The group-level node-roles identification analysis revealed that overall there are more connector hubs and non-hub connector nodes in ASD group in temporal, and frontal areas (b). At group-level, there are more peripheral nodes and provincial hubs in parietal, frontal and temporal areas whereas the ratio of connector hubs and non-hub connectors is limited to occipital cortex, medial temporal and parietal areas. (c), (d) represent the four communities with the distribution of different-node types across seven functional networks. The bigger squares are connector hubs and smaller square are non-hub connector nodes. (e, and f) represent significant connector hubs (bigger sphere) and non-hub connector nodes (smaller sphere) in ASD and TD groups, respectively. (g) There are few significant connector hubs and non-hub connector nodes which are common across both groups.
TABLE 7 A list of connector hubs

| Brain regions | Network  | Hem | x    | y    | z    |
|---------------|----------|-----|------|------|------|
| ASD-specific hubs |          |     |      |      |      |
| Lingual MVocC | Vis L    | −10 | −67  | −4   |      |
| STS           | SM L     | −53 | −24  | 9    |      |
| STS           | SM R     | 51  | −15  | 5    |      |
| dCG           | Sal R    | 7   | 9    | 41   |      |
| TD-specific hubs |        |     |      |      |      |
| mOFG (dmPFC) | DMN L    | −12 | 63   | −6   |      |
| mSFG (dmPFC) | DMN L    | −8  | 59   | 21   |      |
| Common hubs  |          |     |      |      |      |
| dlINS         | Sal R    | 46  | −4   | −4   |      |
| dmPFC         | DMN R    | 8   | 58   | 18   |      |
| STG           | SM L     | −51 | −4   | −2   |      |

Note: Bootstrap method with FDR correction (p < 0.001).
Abbreviations: DA, dorsal-attention; DMN, default-mode; Hem, hemisphere; L, left; Lim, limbic; R, right; Sal, salience; SM: sensorimotor; Vis, visual; xyz, Montreal Neurological Institute template brain (MNI) coordinates.

TABLE 8 A list of non-hub connector nodes

| Brain regions | Network | Hem | x    | y    | z    |
|---------------|---------|-----|------|------|------|
| ASD-specific nodes |        |     |      |      |      |
| vlITG         | DA L    | −57 | −60  | −1   |      |
| FEF           | DA L    | −31 | −4   | 53   |      |
| lOrG          | Lim L   | −24 | 22   | −20  |      |
| cauIFG(PFC)   | DMN L   | −52 | 22   | 8    |      |
| LoCt          | Vis R   | 48  | −71  | −6   |      |
| lvITG         | DA R    | 50  | −53  | −15  |      |
| dlMTG         | DA R    | 52  | −60  | 9    |      |
| FEF           | DA R    | 34  | −4   | 52   |      |
| PrC           | Sal R   | 51  | 4    | 40   |      |
| lMTG          | Lim R   | 30  | 9    | −38  |      |
| CG            | CEN R   | 3   | 3    | 30   |      |
| rosSTG        | DMN R   | 55  | −6   | −10  |      |
| rosIFG (vPFC) | DMN R   | 51  | 28   | 0    |      |
| TD-specific nodes |       |     |      |      |      |
| infLOcC       | Vis     | −27 | −95  | −12  |      |
| rosPhG        | Lim     | −29 | −6   | −39  |      |
| Common-specific nodes |      |     |      |      |      |
| LoCt          | Vis L   | −45 | −69  | −8   |      |
| LoCt          | Vis L   | −47 | −70  | 10   |      |
| lvFuG         | DA L    | −43 | −48  | −19  |      |
| PCL           | Sal L   | −11 | −35  | 46   |      |
| lpPhG         | Vis R   | 39  | −35  | −23  |      |
| PCL           | Sal R   | 11  | −36  | 47   |      |
| lOrG          | Lim R   | 28  | 22   | −19  |      |
| vMFG(PFC)     | CEN R   | 46  | 24   | 26   |      |

Note: Bootstrap method with FDR correction (p < 0.001).
Abbreviations: DA, dorsal-attention; DMN, default-mode; Hem, hemisphere; L, left; Lim, limbic; R, right; Sal, salience; SM: sensorimotor; Vis, visual; xyz, Montreal Neurological Institute template brain (MNI) coordinates.

Alteration in global modularity in ASD

As reported in the previous literature, we observed a reduction in global modularity that might reflect hypersynchronized brain networks (i.e., fewer connections within modules and more connections between modules) in individuals with ASD ranging from 6 to 30 years (Harlalka et al., 2019; Henry et al., 2018; Keown et al., 2017; Rudie et al., 2013). Additionally, we also observed an increase in the number of modules, along with a significant decrease in the modular size in the ASD group, which is indicative of the partitioning of brain networks into modules of smaller sizes in ASD participants compared with TD. These alterations in global modular properties might be reflective of the apparent randomness of functional brain networks previously observed in ASD individuals from 8.5 to 50 years of age (Henry et al., 2018; Keown et al., 2017; Rudie et al., 2013) and might result from alterations in graph-theoretical properties such as reduction in clustering coefficient and characteristic path length as reported in several previous studies of adults (19–51 years) with ASD (Itahashi et al., 2014).

Reduced similarity in modular composition in ASD

Reconfiguration of brain networks might play an integral role in executing cognitive functions. Previous studies report that alterations in modular reconfiguration might be associated with reduced cognitive functioning with age (Meunier et al., 2010) and clinical disorders such as schizophrenia (van den Heuvel et al., 2010). Group-level modular structure composition analysis reflects that both groups shared nearly equal amounts of information, suggesting that at the gross level, functional brain organization is relatively well-preserved in ASD compared with TD.

However, subject-level analyses revealed that significant group differences in community composition reflected an increased heterogeneity (i.e., reduced similarity) in modular composition within ASD compared with...
the TD group. Keown 2017 also showed this reduction in community structure similarity in individuals with ASD. Our study also revealed that global levels of modular reconfiguration and heterogeneity in modular structure in ASD might result from reduced cohesiveness of nodes to their modules across subjects, especially nodes of networks such as DMN, visual, CEN, and SM networks.

Modular cohesiveness of nodes directed by their modular connectivity

Alteration in modular connectivity is essential for the integration and segregation of networks, which permits a reconfiguration of the global modular organizations to perform different types of cognitive tasks such as working memory or finger tapping in adults (22-40 years) (Cohen & D’Esposito, 2016; Stanley et al., 2014; Stevens et al., 2017). Modular connectivity alters the flexibility of the nodes to switch modules to mediate the exchange of information across modules (Harlalka et al., 2019). Our findings show that the increase in between-modular connectivity of nodes belonging to three functional brain networks, namely DMN, SMN, and salience, was negatively associated with their modular cohesiveness. This provides an explanation that these nodes with increased between-module connectivity (BMC) interact more with other modules and thus possibly switch their modules more frequently in the ASD group compared with the TD group. These findings suggest that the altered inter-modular connectivity of DMN, SM, and salience networks not only impacts the overall modular composition but also influences global modularity. Furthermore, this overall increase in BMC along with a reduction in global modularity in the ASD group reflects that the system exhibits less robust modular organization and explains the atypical synchronicity of the functional brain networks reported in ASD individuals.

Nodal roles altered in ASD

The nodes with different functional roles influence the flow of information within and between modules (Luo & Todd Constable, 2022) and thus the proportion of different types of nodes will further influence the global flow of information, efficient integration/segregation of functional brain networks, and cognitive performance (Bertolero et al., 2017; Bertolero et al., 2018). Thus, the proportions of nodes with different topological roles are also considered global properties of modular network organization (Van den Heuvel & Sporns, 2013). To facilitate information flow across and within the modules, different types of nodes have differing abilities to switch modules, thus different node types also have different modular membership consistency (e.g., connector hubs have more flexibility to switch modules and play a crucial role in exchanging information within and across modules).

Our results demonstrate that children with ASD had relatively higher proportions of non-hub connectors (NHC) (responsible for between-module connectivity) and reduced proportions of peripheral non-hubs (NHP) and provincial hubs (HP) (maintain more within-module connectivity) compared with TD children. The follow-up analysis revealed that peripheral nodes in TD converted to non-hub connectors in ASD, whereas provincial hubs converted to connector hubs in ASD. These findings explain the observed increase in between-module connectivity in ASD due to increased proportion of NHC nodes and decreased within-module connectivity due to decreased proportions of HP and NHP.

As reported in previous literature, major common connector hubs were from SM, Sal, and DMN, whereas children with ASD had more connectors from SM and Sal networks (Keown et al., 2017; Ray et al., 2014). These nodes being connectors also had higher flexibility to switch modules, resulting in increased between-modular connectivity. Furthermore, another node type exhibiting increased modular connectivity in ASD was non-connector nodes, from DMN and dorsal attention and limbic networks. These results reflect that major large-scale network-level alterations in children with ASD involve brain regions of the DMN, SM, and Sal networks (Lynch et al., 2013; Marshall et al., 2020; Uddin et al., 2013, 2015; Uddin & Menon, 2009).

Relationship between modular organization and symptom severity

We found that at the nodal level, modular composition and connectivity were associated with ASD symptom severity, while the whole-brain global measures of modular organization did not show significant correlations with ASD symptom severity. This builds on previous literature suggesting that properties of nodal connectivity might be a better reflection of higher cognition such as intelligence as compared with topological properties of global modular network organization (Hilger et al., 2017).

We observe that between-module connectivity in ASD arises from increased proportion of NHC nodes and decreased within-module connectivity due to decreased proportions of HP and NHP. Most notable community membership and nodal discrepancies were contributed by primary visual and speech centers of the brain including areas Lateral Occipital Cortex (LoCe), Fusiform Gyrus (FG), precentral gyrus (PrG), postcentral gyrus (PoG), superior temporal gyrus (STG). The discrepancy in intermodular relationship with core brain areas such as dorso-medial prefrontal cortex (dmPFC),...
precuneus (Pcun), inferior parietal lobule (IPL), and lateral prefrontal cortex (IPFC) suggests the greater the manifestation of social symptom severity the higher the discrepancy in the inter and intramodular organization and reduced global cohesiveness (Hilger et al., 2017; Keown et al., 2017; Roy & Uddin, 2021).

Moreover, our results suggest that overall increase in between module connectivity between DMN, SN and CEN along with a reduction in global modularity in the ASD group reflects that the system exhibits less robust modular organization and explains the atypical synchronicity of the functional brain networks reported in ASD individuals that gives rise to core deficits (Bernhardt et al., 2017; Marshall et al., 2020; Uddin et al., 2013, 2015). The alteration of modular connectivity contributed by dmPFC, Pcun, IPL, and IPFC nodes was also associated with ADOS scores. These results further reinforce the critical role exhibited by the DMN and CEN nodes contributing to atypical modular organization and development of core and peripheral brain network functional organization in ASD during early development (Roy & Uddin, 2021; Uddin et al., 2013, 2015).

Given the lack of developmental consistency in the previous literature exploring global and nodal modular network organization in individuals with ASD, our results provide evidence of atypicality in functional brain modular properties in children with ASD. Aligning with previous studies suggesting atypicality in modular organization in adolescence and adulthood, our findings disentangling detailed nodal roles sculpting distinct global differences in modular cohesiveness between ASD and TD could help further elucidate potential biomarkers and facilitate advancement of intervention strategies and therapies at early developmental stages.

LIMITATIONS

The study was based on multi-site data from ABIDE I and II, thus, to eliminate multi-site covariations we used statistical tests. However, co-variants caused by differing scanning protocols and scanners were not considered. Furthermore, since ASD is more prevalent in males and to avoid co-variants resulting from effects of gender, we focused on male individuals with ASD. Further investigation will be required to study gender effects on modular properties of functional brain networks in ASD. This study had a small sample size thus, the current findings await replication with a larger sample size using data from sites other than ABIDE I and II.

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CONFLICT OF INTEREST

The authors state that there are no biomedical financial interests or potential conflicts of interest, regarding the work presented here, by any of the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Autism Brain Imaging Data Exchange (ABIDE) at https://fcon_1000.projects.nitrc.org/indi/abide/.

ETHICS STATEMENT

Prior to data contribution to ABIDE I & II by the three sites (NYU, Stanford, San Diego) (data used in this study) were required to confirm the clearance from their local institute review board (IRB) or ethics committee. The local ethics committee have approved both the initial data collection and the retrospective sharing of a fully de-identified version of the datasets (i.e., after removal of the 18 protected health information identifiers including facial information from structural images as identified by the Health Insurance Portable and Accountability Act [HIPPA]). All study participants provided written informed assent or consent prior to study participation with parental or legal guardian consent required of all study participants under the age of 18.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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