Aberrant development of the asymmetry between hemispheric brain white matter networks in autism spectrum disorder

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Abstract
Atypical brain asymmetry/lateralization has long been hypothesized for autism spectrum disorder (ASD), and this model has been repeatedly supported by various neuroimaging studies. Recently, hemispheric network topologies have been found to be asymmetric, thereby providing a new avenue for investigating brain asymmetries under various conditions. To date, however, how network topological asymmetries are altered in ASD remains largely unexplored. To clarify this, the present study included ASD individuals from the newly released Autism Brain Imaging Data Exchange II database (58 right-handed male ASD individuals aged 5 to 26 years and 70 age- and IQ-matched typically developing (TD) individuals). Diffusion and structural magnetic resonance imaging were used to construct hemispheric white matter networks, and graph-theory approaches were applied to quantify topological efficiencies for hemispheric networks. Statistical analyses revealed a decreased rightward asymmetry of network efficiencies with increasing age in the TD group, but not in the ASD group. More specifically, the TD group did not exhibit an age-related increase in network efficiency in the right hemisphere, but the ASD group did. For the left hemisphere, no difference between the groups was observed for the developmental trajectory of network efficiencies. Intriguingly, within the ASD group, more severe restricted and repetitive behaviors were correlated with a less pronounced decrease in network efficiency with increasing age.
behavior in ASD was found to be correlated with less rightward asymmetry of network local efficiency. These findings provide suggestive evidence of atypical network topological asymmetries and offer important insights into the abnormal development of ASD brains.

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1. Introduction

As a severe neurodevelopmental disorder, autism spectrum disorder (ASD) is characterized by impairments in language and social interaction and by the presence of repetitive and stereotypical behaviors (American Psychiatric Association, 2000; Kanner, 1943). Various psychopathological hypotheses have been proposed for ASD, one of which involves hemispheric asymmetry/lateralization (Kleinhans et al., 2008). According to this hypothesis, there should be a loss or inversion of typical patterns of brain lateralization/asymmetry in ASD patients (Floris et al., 2013; Lo et al., 2011).

Numerous lines of neuroimaging evidence have supported this hypothesis. For example, early PET studies showed atypical or reversed cerebral blood flow in frontal language regions (Chiron et al., 1995; Müller et al., 1999; Ohnishi et al., 2000). Functional MRI techniques further revealed ASD-related atypical rightward lateralization of functional language, motor, and visuospatial networks, as well as of the default-mode network (Cardinale et al., 2013; Floris et al., 2016b; Lindell and Hudry, 2013; Nielsen et al., 2014). Structurally, there have been reports of abnormal volumetric asymmetry patterns observed in frontal and temporal lobes in ASD (Herbert et al., 2002; Herbert et al., 2005; Rojas et al., 2002; Rojas et al., 2005). In addition, white matter (WM) tracts, e.g., the arcuate fasciculus (AF) and uncinate fasciculus (UF), have been reported to exhibit atypical asymmetry patterns of diffusion MRI indices (e.g., FA) in ASD (Fletcher et al., 2010; Knaus et al., 2010; Lo et al., 2011). Furthermore, a few studies reported significant correlations between atypical asymmetry and behavioral/cognitive deficits in ASD. For instance, there was a significant correlation between the motor performance and hemispheric lateralization: more rightward asymmetry of the functional correspondence within the motor network was associated with poorer motor performance in ASD patients (Floris et al., 2016a).

In recent years, multimodal MRI techniques have been extensively applied to model the human brain as a complex network of brain regions connected by anatomical tracts or functional associations, with graph theoretical approaches being subsequently used to reveal the topological organization for the constructed brain networks (Iturria-Medina et al., 2007; Rubinov and Sporns, 2010). Several studies have demonstrated whole-brain network topological differences between ASD and typically developing (TD) individuals, e.g., differences in network clustering, path length, modularity, and rich-club/hub organization (Itahashi et al., 2014; Li et al., 2014a; Rudie et al., 2013).

In addition to the whole-brain network topological organization, hemispheric network topologies are also of great importance. In particular, they can provide a novel network topological perspective for studying brain asymmetries. Several reports have revealed significant topological asymmetries between hemispheric structural networks in healthy populations (Iturria-Medina et al., 2011; Li et al., 2014b; Ratnarajah et al., 2013). In ASD studies, a few studies have started to examine atypical asymmetries of network connections/nodes between the two hemispheres (Conti et al., 2016). However, the asymmetries of topological properties for the entire hemispheric networks remain largely unexplored.

To clarify these properties, the present study applied diffusion MRI to specifically investigate the asymmetries of network topology between the two hemispheres in ASD. Given the well-demonstrated anomalous brain developmental trajectory in ASD, as well as the reported developmental changes in topological asymmetries of hemispheric networks in healthy subjects (Caeyenberghs and Leemans, 2014; Zhong et al., 2017), we hypothesized a significant age-dependent alteration in the network topological asymmetries in ASD compared with TD individuals. Such differences in asymmetry might serve as structural substrates for specific types of cognitive/behavioral deficits in ASD. Specifically, we constructed hemispheric WM networks in a relatively large cohort ranging in age from young childhood to young adults, using the newly released Autism Brain Imaging Data Exchange II (ABIDE II) database. Graph theoretical approaches were then applied to quantify multiple topological parameters for hemispheric WM networks.

2. Experimental procedures

2.1. Participants

All samples were selected from the ABIDE II project (Di Martino et al., 2017). There were five imaging sites containing both T1 and diffusion-weighted images. In total, this database contains 155 ASD individuals and 129 TD individuals with the two image modalities. As with other ABIDE studies (Alaerts et al., 2015; Di Martino et al., 2014; Haar et al., 2016), the inclusion criteria for sample selection in the present study were as follows: (i) right-handed males; (ii) individuals with higher full-scale IQ (FSIQ) scores (> 70); (iii) no medication; and (iv) younger than 26 years old. Given the much higher ASD incidence in male than female and the gender effects on the asymmetry, only males were included in this study. There are total 141 subjects (69 ASD patients; 72 TD individuals) meet these inclusion criteria. Next, visual inspection for image quality control excluded 11 individuals (9 ASD patients; 2 TD individuals), whose images have severe image artifacts, head motion, or missing slices. Finally, all individuals from the same imaging site were further excluded if the site had less than 15 individuals in total according to above criteria. In the end, 128 individuals (58 ASD patients; 70 TD individuals) from four imaging sites were entered into our analysis in the present study (for details, see Table 15). The 4 imaging sites were Trinity Center for Health Sciences (TCHS), San Diego State
Table 1. Demographics and clinical scores.

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>TD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>12.19 ± 5.54</td>
<td>13.76 ± 4.69</td>
<td>0.085</td>
</tr>
<tr>
<td>FSIQ</td>
<td>108.48 ± 16.14(58)</td>
<td>112.26 ± 14.55(70)</td>
<td>0.167</td>
</tr>
<tr>
<td>VIQ</td>
<td>108.31 ± 15.96(52)</td>
<td>113.65 ± 15.37(60)</td>
<td>0.074</td>
</tr>
<tr>
<td>PIQ</td>
<td>108.29 ± 18.26(52)</td>
<td>108.65 ± 15.31(60)</td>
<td>0.909</td>
</tr>
<tr>
<td>ADOS-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>13.43 ± 4.67(35)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>SOCAFFECT</td>
<td>10.17 ± 3.83(35)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>RRB</td>
<td>3.26 ± 1.88(35)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

For each group, the numbers of subjects, mean and standard deviation of age, IQ scores and ADOS-2 scores are presented. The numbers in parentheses indicate the numbers of subjects who successfully performed the IQ test and the ADOS-2 assessment. FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; ADOS-2 = Autism Diagnostic Observation Schedule-2nd Edition; SOCAFFECT = Social Affect; RRB = Restricted, Repetitive Behaviors.

University (SDSU), Barrow Neurological Institute (BNI), and New York University Langone Medical Center (NYU). The ASD and TD groups were matched overall in age and IQ, and also within each site (Table 1 and Table 1S).

All ASD patients had a DSM-IV-TR diagnosis of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder-Not Otherwise Specified, established by expert clinical opinion aided by the multidisciplinary clinical “gold standard” instruments of the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord et al., 2012; Aoki et al., 2017), and/or the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994). Briefly, the ADOS uses direct observation by specially trained objective professionals in a standardized format of activity; the researcher observes the interactions, communication and any atypical repetitive behaviors of the ASD patients. The ADI-R is a semi-structured interview with the individual's primary caregivers focusing on the quality of social interaction, communication and language, and repetitive, restricted interests and behavior.

All data are fully anonymized with no inclusion of protected health information in accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines. The ethical guidelines were followed in accordance with the Institutional Review Boards (IRB) of participating institutions. All ASD patients had a DSM-IV-TR diagnosis of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder-Not Otherwise Specified, established by expert clinical opinion aided by the multidisciplinary clinical “gold standard” instruments of the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord et al., 2012; Aoki et al., 2017), and/or the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994). Briefly, the ADOS uses direct observation by specially trained objective professionals in a standardized format of activity; the researcher observes the interactions, communication and any atypical repetitive behaviors of the ASD patients. The ADI-R is a semi-structured interview with the individual's primary caregivers focusing on the quality of social interaction, communication and language, and repetitive, restricted interests and behavior.

2.2. MRI data acquisition

For the ABIDE II project, the shared MRI data from the four imaging sites were acquired using a 3-Tesla scanner. Specific imaging scanning parameters for each site are listed in Supplementary Tables 2 and 3. More details regarding data acquisition are available on the ABIDE II website.

2.3. Hemispheric brain WM network construction

To study topological asymmetries of hemispheric WM networks in ASD patients and TD individuals, we constructed right- and left-hemispheric networks separately for each individual, following our previously published approach (Zhong et al., 2017). The concise procedures are described below.

2.3.1. Data pre-processing

Imaging pre-processing were conducted using by the PANDA, a pipeline toolbox for analyzing brain diffusion images), including brain extraction, correction for simple head motion and eddy current distortions, correction for b-matrix (Cui et al., 2013).

2.3.2. Hemispheric network construction

Like other complex networks, a brain network consists of two basic types of elements: nodes and edges. To define the nodes, the AAL template in the Montreal Neurological Institute (MNI) space was first binarized, excluding the cerebellum. The resultant mask and its flipped version were combined to yield a symmetric mask for the entire cerebral cortex. A random partitioning process (Zalesky et al., 2010) was then utilized to parcelate the right hemispheric part of the mask into 512 uniform regions of interest (ROIs); the resultant 512-ROI set in the right side was then flipped into the left hemisphere, which ensured a one-to-one ROI correspondence between the right and left hemispheres. Next, the symmetric 1024-ROI set in the MNI space were transformed to the native space for each subject, as described previously (Gong et al., 2009). Specifically, the native T1 image of each subject was first nonlinearly normalized to the symmetric ICBM-152 T1 template in the MNI space. Notably, this symmetric T1 template in the standard space was used to guarantee that the two hemispheres of each subject were mapped to the same target hemispheric template, therefore establishing the spatial correspondence of homogeneous areas between the two hemispheres. The resultant spatial non-linear transformation was inverted and then applied to the symmetric 1024-ROI set in the MNI space, resulting in the native space parcellation for each subject.

The edges between every pair of the 512 ROIs within a hemisphere were estimated using probabilistic fiber tractography implemented in the FSL software package (available at http://www.fmrib.ox.ac.uk/fsl/). Specifically, we first estimated voxel-wise probability density functions (PDFs) by Markov Chain Monte Carlo sampling with a 2-fiber model. Then, the probabilistic tractography were conducted by seeding from each node and sampling 5000 tracts for each voxel within the seed region with a step length of 0.5 mm. For each sample, the principal diffusion direction was determined from the local PDF. This process stopped when it reached the boundary of brain, or the path loops back to itself, or the curvature exceeded 0.2. The edge weight was defined as the connectivity probability from region i to region j after correcting for the distance (Chu et al., 2015). For each subject, the above approach yielded two separate $512 \times 512$ symmetric weighted matrices, each representing a hemispheric network of the human brain.
2.4. Network topological parameters

Graph theoretical analysis provides a powerful mathematical tool for characterizing the topological properties of brain networks (Bullmore and Sporns, 2009; He et al., 2007). As in our previous study (Zhong et al., 2017), we focused on the parameters related to topological efficiency: network global efficiency, network local efficiency, nodal global efficiency, and nodal local efficiency. These parameters were computed using the Gretna package (Wang et al., 2015) and are introduced below.

2.4.1. Nodal global efficiency

Nodal global efficiency represents the capacity of a node to communicate with the other nodes of a network. For a particular node \( i \), the nodal global efficiency is defined as follows:

\[
E_{\text{global}}^G(i) = \frac{1}{N-1} \sum_{j \neq i} \frac{1}{d_{ij}}
\]

where \( L_{ij} \) is the shortest path length between node \( i \) and node \( j \), and \( N \) denotes the number of nodes in the network \( G \).

2.4.2. Network global efficiency

Network global efficiency is a global measure of the information transfer ability of the entire network, which is computed as the mean of the nodal global efficiencies of all nodes within the network (Latora and Marchiori, 2001):

\[
E_{\text{global}}^G = \frac{1}{N(N-1)} \sum_{i=1}^{N} \sum_{j=1, j \neq i}^{N} \frac{1}{L_{ij}}
\]

2.4.3. Nodal local efficiency

Nodal local efficiency represents the communication capacity of the sub-network composed of the nearest neighbors of a node. The nodal local efficiency for node \( i \) is defined as follows:

\[
E_{\text{local}}^G(i) = E_{\text{global}}^G
\]

where \( G_i \) is the neighborhood sub-network for the node \( i \).

2.4.4. Network local efficiency

Network local efficiency corresponds to the average efficiency of information flow within the local environment and reflects the average ability of a network to tolerate faults (Latora and Marchiori, 2001). The local efficiency of a network is computed as the mean of the nodal local efficiencies of all nodes within the network:

\[
E_{\text{local}}^G = \frac{1}{N} \sum_{i=1}^{N} E_{\text{local}}^G(i)
\]

2.5. Asymmetry index

To quantify hemispheric differences in these topological efficiency parameters, we computed an asymmetry index (AI) to characterize the degree of asymmetry, as follows: \( AI = \frac{E_{\text{global}}^G(L) - E_{\text{global}}^G(R)}{E_{\text{global}}^G(L) + E_{\text{global}}^G(R)} \), where \( E_{\text{global}}^G(L) \) and \( E_{\text{global}}^G(R) \) are the efficiency parameters of the left- and right-hemispheric networks, respectively. For each subject, there is one AI value for hemispheric network global efficiency or network local efficiency, but there are 512 AI values for nodal global efficiency or nodal local efficiency, each corresponding to a network node. Here, a positive AI value indicates a prominent leftward asymmetry, and a negative value indicates the opposite.

2.6. Statistical analysis

To evaluate group differences in age and FSIQ, two-sample t tests were performed.

We first tested whether there was a significant lateralization of network efficiencies (i.e., the AI scores are significantly different from zero) in both groups. Then, we evaluated whether there are group differences in the developing trajectory for the AI values network properties (i.e., network global efficiency, network local efficiency, 512 nodal global efficiencies, and 512 nodal local efficiencies). To that end, we assessed the group \( \times \) age interaction effects on AI values for each of those topological efficiency parameters. Specifically, a general linear model (GLM) with “age”, “group”, and “group \( \times \) age” as predictor variables was applied. Notably, network efficiency parameters were found to be significantly associated with brain size (Yan et al., 2011). In addition, the two hemispheres differed significantly in size (Giedd et al., 1996), and the difference of network efficiency parameters therefore may relate to size difference between the two hemispheres. To control for these brain size related confounding effects, intracranial volume (ICV) and difference in hemispheric ICV were included as covariates, same as our previous study (Zhong et al., 2017). Here, the ICV was composed of gray matter (GM), WM and cerebrospinal fluid (CSF), which were segmented in T1 images using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). In addition, given the differences in MRI scanner types and imaging parameters among imaging sites, the imaging site was also included as a covariate in the statistical model, as did in previous studies (Hahamy et al., 2015). For the AIs of nodal efficiencies, the false discovery rate (FDR) method was applied to correct for multiple comparisons across all nodes (Genovese et al., 2002), and \( q < 0.05 \) was considered significant.

A significant group \( \times \) age interaction on the AI suggests a difference in such an interaction between the two hemispheres. To ascertain how the two hemispheres differ in this interaction, we applied post hoc analyses to evaluate the group \( \times \) age interaction effects on the absolute topological parameters for each hemisphere, in case of a significant group \( \times \) age interaction on the AI for this topological parameter. Similarly, a GLM with “age”, “group”, and “group \( \times \) age” as predictor variables was applied. As explained above, hemispheric ICV and imaging site were included as covariates to control for the confounding effects of brain size and MRI protocol differences, respectively.

Finally, we explored the associations between the AI of topological efficiencies and clinical scores measured by the ADOS-2nd edition (ADOS-2) in the ASD group. The ADOS-2 was chosen because it was a more objective assessment than the ADI-R (Lemler, 2012) and is an updated revision of ADOS-Generic edition (ADOS-G) (Lord et al., 2012). Specifically, we focused on three specific ADOS-2 scores: the total score (Total), social affect (SOCAFFECT) score, and restricted, repetitive behaviors (RRB) score. Higher SOCAFFECT score represents poorer communication and reciprocal social interaction, and higher RRB score reflects poorer repetitive behavior performance. The correlational analyses were applied after controlling for age, imaging site, ICV, difference in hemispheric ICV, and FSIQ. For the network efficiencies, the Bonferroni correction was used to correct for multiple comparisons for the 3 diagnostic test scores, i.e., uncorrected \( p < 0.05/3 \). For the nodal efficiencies, the correlational analyses were restricted to the nodes/ROIs showing a significant group \( \times \) age interaction effect (thus putatively ASD-disease related). The FDR method was applied to correct for multiple comparisons across the significant nodes (Genovese et al., 2002), and \( q < 0.05/3 \) was considered significant (i.e., the Bonferroni correction was also applied for the 3 diagnostic scores). All statistical analyses were conducted using SurfStat for MATLAB (Worsley et al., 2009).
2.7. Replication validation

In the present study, we used a random parcellation procedure to define network nodes. To evaluate the robustness of our findings, we applied another random parcellation procedure using the exact same procedure and repeated the hemispheric brain network analyses as above. Here to distinguish the 2 random parcellation schemes, we designated the original one as parcellation I and the scheme used for validation as parcellation II.

3. Results

3.1. Site differences

According to the Chi-square test, the control/patient group did not differ significantly across sites (\( p = 0.24 \)). Regarding the age, there was a significant site difference (\( F = 52.39; p = 0.001 \)). Neither the AI of network local efficiency nor the AI of network global efficiency showed any significant site difference, after controlling for group (AI of network local efficiency: \( F = 1.75, p = 0.161 \); AI of network global efficiency: \( F = 1.54, p = 0.21 \)) or not (AI of network local efficiency: \( F = 1.76, p = 0.16 \); AI of network global efficiency: \( F = 1.57, p = 0.20 \)). Notably, only ASD participants had the diagnostic scores, and there was a marginally significant site difference in the Total (\( F = 3.19, p = 0.055 \)) and the SOCIAFFECT score (\( F = 3.33, p = 0.049 \)), but not in the RRB score (\( F = 1.20, p = 0.31 \)).

3.2. Within-group asymmetry of network efficiencies

A mixed-effect GLM was applied to hemispheric network parameters, in which the hemisphere was taken as a repeated measure, and imaging site, ICV, and difference in hemispheric ICV were included as covariates. Significant rightward lateralization in both network local efficiency (\( t = -2.72, p = 0.0075 \)) and network global efficiency (\( t = -2.12, p = 0.036 \)) was observed in the TD group. In the ASD group, we also observed a significant rightward lateralization in the network local efficiency (\( t = -2.38, p = 0.019 \)) but not in the network global efficiency (\( t = 0.019, p = 0.99 \)). After further controlling for age, the statistical significance remained the same (the TD group, network local efficiency: \( t = -2.68, p = 0.0083 \), network global efficiency: \( t = -2.10, p = 0.038 \); the ASD group, network local efficiency: \( t = -2.36, p = 0.020 \), network global efficiency: \( t = -0.063, p = 0.95 \)).

3.3. Group × age interaction effects on the AI of network efficiencies

As shown in Table 2 and Figure 1, there was a significant group × age interaction effect on the AI for both network local efficiency (\( F = 4.6; p = 0.034 \)) and network global efficiency (\( F = 5.68; p = 0.019 \)), suggesting a significant group difference in the association between the AI of network efficiencies and age. Post hoc analysis revealed significant positive correlations between age and the AI of both network local efficiency (\( r = 0.23, p = 0.047 \)) and network global efficiency (\( r = 0.44, p = 0.001 \)) in the TD group but not in the ASD group (network local efficiency: \( r = -0.14, p = 0.29 \); network global efficiency: \( r = 0.049, p = 0.72 \)). As illustrated in Figure 1, TD individuals exhibited a reduced rightward asymmetry for both the network local efficiency and network global efficiency as age increased, but there was no such developmental trajectory in ASD patients.

In addition, we reran our above analyses without controlling for ICV and difference in hemispheric ICV. The

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Statistical results using the 2 Parcellation schemes.</th>
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<tbody>
<tr>
<td></td>
<td>Parcellation I</td>
</tr>
<tr>
<td></td>
<td>F-value</td>
</tr>
<tr>
<td>AI of network efficiencies</td>
<td>( F )-value</td>
</tr>
<tr>
<td>Network local efficiency</td>
<td>4.6</td>
</tr>
<tr>
<td>Network global efficiency</td>
<td>5.68</td>
</tr>
<tr>
<td>Network efficiency for each hemisphere</td>
<td></td>
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<tr>
<td>Network local efficiency of the left hemisphere</td>
<td>0.52</td>
</tr>
<tr>
<td>Network global efficiency of the left hemisphere</td>
<td>1.03</td>
</tr>
<tr>
<td>Network local efficiency of the right hemisphere</td>
<td>4.37</td>
</tr>
<tr>
<td>Network global efficiency of the right hemisphere</td>
<td>11.15</td>
</tr>
<tr>
<td>The mean AI of nodal efficiencies across identified nodes/ROIs</td>
<td></td>
</tr>
<tr>
<td>Nodal local efficiency</td>
<td>9.58</td>
</tr>
<tr>
<td>Nodal global efficiency</td>
<td>23.46</td>
</tr>
<tr>
<td>The mean nodal efficiency for each hemisphere</td>
<td></td>
</tr>
<tr>
<td>Nodal local efficiency of the left hemisphere</td>
<td>0.53</td>
</tr>
<tr>
<td>Nodal global efficiency of the left hemisphere</td>
<td>1.03</td>
</tr>
<tr>
<td>Nodal local efficiency of the right hemisphere</td>
<td>4.67</td>
</tr>
<tr>
<td>Nodal global efficiency of the right hemisphere</td>
<td>23.76</td>
</tr>
</tbody>
</table>

\( AI \) = asymmetry index.
statistical significance remained unchanged: there was a significant group × age interaction effect on the AI for both network local efficiency (F = 4.92; p = 0.029) and network global efficiency (F = 6.79; p = 0.010).

Finally, we additionally evaluated whether there was a main group effect on the AI scores, after controlling for imaging site, ICV and difference in hemispheric ICV. The statistical results showed no significant group difference (AI of network local efficiency: t = 0.31, p = 0.76; AI of network global efficiency: t = 1.49, p = 0.14). After further controlling for age in the statistical model, we observed similar non-significant results (AI of network local efficiency: t = 1.85, p = 0.067). These additional results suggested that regressing out these covariates or not had a very limited impact on our results.

3.4. Group × age interaction effects on hemispheric network efficiencies

Given the observed significant group × age interaction on the AI for both network local efficiency and network global efficiency, we further assessed this interaction in terms of the network local efficiency and the network global efficiency of each hemisphere, separately, to ascertain how the two hemispheres differ in this interaction. Specifically, we found a significant group × age effect for the right hemisphere (network local efficiency: F = 4.37, p = 0.039; network global efficiency: F = 11.15, p = 0.001) but not for the left hemisphere (network local efficiency: F = 0.52, p = 0.47; network global efficiency: F = 1.03, p = 0.312; Figure 2), indicating aberrant development of the right hemisphere in the ASD group compared with the control group. For the significant group × age effect on the network global efficiency of right hemisphere, post hoc analysis revealed a significant positive correlation between right-hemispheric network global efficiency and age in the ASD group (r = 0.44, p < 0.001) but no significant correlation in the TD group (r = 0.013, p = 0.92). Similarly, a trend for a positive correlation was observed in the ASD group (r = 0.25, p = 0.057) for the right-hemispheric network local efficiency, but not in the TD group (r = 0.014, p = 0.91). Regarding the left hemisphere, no significant correlation between age and the network local efficiency was observed in either group (ASD: r = 0.17, p = 0.21; TD: r = 0.17, p = 0.15), but there was a positive correlation of the network global efficiency with age (ASD: r = 0.51, p < 0.001; TD: r = 0.42, p < 0.001; Figure 2).

According to the visual inspection, the significant correlation within the ASD group was possibly caused by the two older ASD subjects. To test this, we re-did the above analysis after removing the two older ASD subjects. The results showed that only the statistical significance of the group × age effect on the network local efficiency for the right hemisphere was changed from significant (p = 0.039) to non-significant (p = 0.15), and all the other statistical significance remained the same (data not shown), supporting the validity of our results.

Finally, our additional analyses without controlling for hemispheric ICV showed similar statistical results: there was a significant group × age interaction effect for the right hemisphere (network local efficiency: F = 4.46, p = 0.037; network global efficiency: F = 11.46, p < 0.001) but not for the left hemisphere (network local efficiency: F = 0.57, p = 0.45; network global efficiency: F = 1.05, p = 0.309), which indicates a very limited effect of hemispheric ICV on our results.
3.5. Group × age interaction effects on the AI of nodal efficiencies

The ROI-wise F maps for the group × age interaction effect on the AI of nodal local efficiency and nodal global efficiency are illustrated in Figure 3A and Figure 4A, respectively. No nodes/regions survived a strict FDR-based correction for multiple comparisons. We therefore lowered the significance threshold to the level of uncorrected $p < 0.01$ and identified brain regions surviving that threshold. For the AI of nodal local efficiency, the identified nodes/regions were mainly located around the rectus, orbital portions of the middle frontal gyrus, supramarginal gyrus, postcentral gyrus, inferior parietal lobule, precuneus, angular gyrus, insula, putamen, and pallidum (Figure 3B). For the AI of the nodal global efficiency, the regions were predominantly located in the triangular part of the inferior frontal gyrus, the orbital part of the middle frontal gyrus, the Rolandic operculum, the posterior superior and middle temporal gyrus, insula, and thalamus (Figure 4B).

Using the mean AI of nodal efficiencies across all of the above identified nodes/regions, we illustrated the scatter plots for the group × age interaction effect in Figure 3C and Figure 4C: nodal local efficiency: $F = 9.58$, $p$...
Aberrant brain white matter network asymmetry in ASD

Figure 3  The group × age interaction effects on the mean AI of the hemispheric nodal local efficiency and the mean absolute nodal local efficiency of the two hemispheres. (A) The F statistic map for the group × age interaction. (B) The regions showing significant group × age interaction effects on the mean AI of the nodal local efficiency at the uncorrected p < 0.01 level, after controlling for imaging site, ICV, and the difference in hemispheric ICV. (C) Scatter plot of the group × age interaction effects on the mean AI of nodal local efficiency. (D) The group × age interaction effects on the mean nodal local efficiency of the left hemisphere. (E) The group × age interaction effects on the mean nodal local efficiency of the right hemisphere. For the hemispheric topological properties, statistical analyses were conducted after adjusting for imaging site and the hemispheric ICV.

Post hoc analysis indicated that with increasing age, TD individuals exhibited a significantly reduced rightward asymmetry for both the mean AI values of nodal efficiency (nodal local efficiency: $r = 0.35, p = 0.003$; nodal global efficiency: $r = 0.44, p < 0.001$). In contrast, with increasing age, ASD patients showed an increased rightward asymmetry in the nodal global efficiency ($r = -0.33, p = 0.01$) but no significant changes in the nodal local efficiency ($r = -0.20, p = 0.14$).

Furthermore, the group × age interaction effect on the mean nodal efficiencies of these identified nodes for each hemisphere was investigated. As illustrated in Figure 3D and E and Figure 4D and E, the right hemisphere showed a significant interaction effect on the mean nodal efficiencies (nodal local efficiency: $F = 4.67, p = 0.036$; nodal global efficiency: $F = 23.76, p < 0.001$), whereas no significant interaction effects were observed within the left hemisphere (nodal local efficiency: $F = 0.53, p = 0.47$; nodal global efficiency: $F = 1.03, p = 0.31$). Specifically, for the right hemisphere, the mean nodal global efficiency increased significantly with age in ASD individuals ($r = 0.48, p = 0.001$), whereas that of TD individuals decreased significantly ($r = -0.26, p = 0.03$); the mean nodal local
efficiency in ASD and TD individuals showed opposite trends but no significant effect of age (ASD: $r = 0.22$, $p = 0.09$; TD: $r = -0.06$, $p = 0.61$). Regarding the left hemisphere, no significant age effect on mean nodal local efficiency was observed in either the ASD group or the TD group (ASD: $r = 0.19$, $p = 0.16$; TD: $r = 0.12$, $p = 0.33$), while a significant age effect on the mean nodal global efficiency was observed in the TD group but not in the ASD group (ASD: $r = 0.20$, $p = 0.13$; TD: $r = 0.38$, $p = 0.001$). Overall, all of these nodal efficiency patterns were largely in agreement with the above results for network efficiencies.

### 3.6. Association between topological asymmetry and ASD clinical scores

Within the ASD group, we did not find significant correlations between age and ADOS-2 scores (Total score: $r = 0.005$, $p = 0.977$; SOCAFFECT score: $r = 0.005$, $p = 0.978$; RRB score: $r = 0.002$, $p = 0.989$). Additionally, we did not observe any $AI \times age$ interaction effects for any of the three ADOS-2 scores (network local efficiency: $Total F = 0.11$, Total $p = 0.75$; SOCAFFECT $F = 0.26$, SOCAFFECT $p = 0.61$; RRB $F = 0.21$, RRB $p = 0.65$; network global efficiency: $Total F$...
After controlling for age, imaging site, ICV, difference in hemispheric ICV, and FSIQ, no significant correlation was observed between the AI of network local efficiency and the ADOS-2 total score or the SOCAFFECT score, with the exception of a positive correlational trend between the AI of network local efficiency and the RRB for the putamen ($r = 0.50; p = 0.0022$; Figure 5A). Intriguingly, the AI of the network local efficiency ($r = 0.50; p = 0.0022$; Figure 5B) and of specific nodal local efficiencies (Pallidum: $r = 0.51; p = 0.0022$; Putamen: $r = 0.58; p < 0.001$; FDR corrected $p < 0.05$; Figure 5C and D) were significantly positively correlated with the RRB score (surviving the Bonferroni correction), indicating that lower levels of right asymmetry were associated with more severe symptoms in restricted and repetitive behaviors. In addition, no significant correlation was observed between the ADOS-2 scores and the absolute network efficiencies for each hemisphere, as shown in Table 4S.

3.7. Validation results with the other Parcellation scheme

For both network and nodal efficiencies, the statistical results for parcellation scheme II were largely consistent
with those for parcellation scheme I (Table 2), supporting the robustness of our current findings.

4. Discussion

Using a cross-sectional sample from the ABIDE II repository, our present study revealed an age-dependent aberration in topological asymmetries for brain WM networks in ASD and also found associations between topological asymmetries and symptom severity within the ASD group. Specifically, with increasing age, there were reduced rightward asymmetries of network efficiencies in TD controls but not in the ASD group. At the hemispheric level, significant group differences in developmental patterns of the network efficiencies were observed in the right hemisphere, with the ASD group showing an age-related increase in the network efficiencies and the TD group showing no such increase. In contrast, the left hemisphere did not exhibit such age-dependent group differences. Intriguingly, more severe restricted and repetitive behavior in ASD, as measured by the ADOS-2-RRB score, was correlated with less rightward asymmetry of network local efficiency within the ASD group. These findings provide direct evidence of atypical topological asymmetry in the ASD group, and this asymmetry likely contributes to the developmental cascade of behavioral and neurological abnormalities.

4.1. Atypical developmental trajectory of hemispheric network asymmetries in ASD

Numerous lines of evidence has shown altered developmental trajectories of various brain measures in ASD, including brain size, cortical thickness, surface area, and WM diffusion parameters (Hardan et al., 2009; Keller et al., 2007; Langen et al., 2014; Mak-Fan et al., 2012; Mengotti et al., 2011; Schumann et al., 2010). In line with this, over- and under-connectivity in ASD have also been reported to be age-specific (Uddin et al., 2013), and local connectivity in ASD has been reported to show a differential developmental trajectory compared with TD individuals (Dajani and Uddin, 2016). Moreover, age-dependent abnormalities of brain asymmetries have been reported in ASD. For example, Dougherty and colleagues showed a reduced leftward asymmetry of the fusiform gyrus with increasing age in ASD but a greater leftward asymmetry with increasing age in TD (Dougherty et al., 2016).

Regarding the whole-brain network, an atypical developmental trajectory of global efficiency of the whole-brain WM network has been observed in ASD: the global efficiency increased with age in TD but decreased with age in ASD (Rudie et al., 2013). Compatible with these results, our study further revealed an abnormal developmental trajectory in the asymmetry of network efficiencies, further supporting an “immature” or aberrant developmental process in ASD. The atypical developmental trajectory in network asymmetries observed in ASD may result from genetics or from compensatory mechanisms/behavioral abnormalities underlying impaired information processing (Dougherty et al., 2016; Hahamy et al., 2015; Sharda et al., 2016).

Notably, ASD is an early-onset neurodevelopmental disorder, and longitudinal MRI studies of infants at high familial risk of developing ASD suggest that differences in the ASD brain can already be seen in the first 2 years of life (Hazlett et al., 2011; Schumann et al., 2010). Therefore, atypical brain asymmetry might be already present in younger ASD children than our current samples. It would be intriguing in the future to discover the timing of the age of onset for the abnormal topological asymmetries in ASD by using infant/toddler MRI data.

At the regional level, there have been reports of atypical developmental trajectories in ASD for the putamen (Langen et al., 2009), fusiform gyrus (Dougherty et al., 2016), and precuneus (Jiang et al., 2015). Consistent with these findings, a number of brain regions in the present study exhibited tendencies toward atypical development of asymmetry in nodal efficiencies, mainly involving the orbitofrontal cortex, anterior middle frontal gyrus, posterior middle temporal gyrus, angular gyrus, insula, thalamus, and putamen. Most of these regions have been identified in previous ASD asymmetry studies. For example, atypical symmetry in cortical language network regions, including the Rolandic operculum, the angular gyrus, and the triangular part of the inferior frontal gyrus, have been suggested to underlie social communication and language deficits in ASD (Floris et al., 2016b). Deficits in frontotemporal regions such as the medial frontal gyrus and the middle and superior temporal gyrus are putatively associated with abnormal socio-emotional processing in ASD (Boddaert et al., 2004; Rojas et al., 2006). In addition, impairment in the frontostriatal system, including the putamen, has been found to mediate repetitive and stereotyped behaviors in ASD (Langen et al., 2014), and changes in the thalamus have been associated with the motor and attentional abnormalities observed in ASD (Nair et al., 2013).

4.2. Aberrant right-hemisphere development in ASD

There has been a longstanding argument that the right hemisphere is more important for global or parallel processing than the left hemisphere (Delis et al., 1986). Suppressed activity in regions of the right hemisphere has been proposed to underlie the prominent piecemeal processing as well as repetitive stereotyped behavior in ASD (Brugger et al., 1996), and rightward asymmetry has been explicitly hypothesized to be a fundamental characteristic of cerebral organization in ASD (Cardinale et al., 2013).

In line with these notions, our data revealed no significant group × age interaction effect on the efficiencies of the left hemisphere in the TD and ASD groups; conversely, the efficiency of the right hemisphere showed a significant interaction effect, with efficiencies showing no age effect in TD but an increase with age in ASD. This indicated an aberrant topological development of the right hemisphere in ASD. In line with this, aberrant development of the right hemisphere in ASD brain has been repeatedly observed in diffusion MRI parameters (Keller et al., 2007; Mengotti et al., 2011), cortical morphology (Raznahan et al., 2010; Zielinski et al., 2014), and functional connectivity (Alaerts et al., 2015). In particular, increased efficiency of the right hemisphere has been observed in healthy carriers with an
ASD risk genotype (Dennis et al., 2011). In contrast to our current observations of age-dependent abnormalities in the right hemisphere, Dean and colleagues reported an age-independent lower network efficiency in the right hemisphere in ASD patients ranging from 3 to 36 years old (Dean et al., 2016). This discrepancy is likely attributable to substantial methodological differences in constructing the hemispheric WM network (WM networks were constructed by correlating tract properties across subjects in Dean et al., 2016), as well as differences in age range.

4.3. Degree of asymmetries correlates with symptom severity of ASD

The ASD-related atypical lateralization would be more strongly supported by a correlation with the clinical severity of the disease. Here, a significant positive correlation was detected between the network local efficiency and the RRB subscale of the ADOS-2, which represents the severity of restricted, repetitive behavior. This further supports the idea that lateralized deficits are related to the prominent piecemeal processing as well as the repetitive stereotyped behavior in ASD (Brugger et al., 1996).

At the regional level, the pallidum and putamen exhibited similar significant positive correlations between the AI of the nodal local efficiency and RRB score. These results are not unexpected because impairment of the frontostriatal circuit, including the putamen, has been reported to be important for the symptoms of ASD, particularly the stereotyped, repetitive, and rigid behavior (Langen et al., 2014; Langen et al., 2012). The restricted, repetitive behaviors of ASD patients have also been found to be positively correlated with the surface area of the dorsal pallidum (Schuetze et al., 2016) and with the functional connectivity of the precuneus (Lee et al., 2016). The observed correlations between asymmetry and RRB in our study indicated a potential role for the atypical asymmetry as a neurobiological marker for ASD.

4.4. Limitation and future work

A few issues should be addressed. First of all, four imaging sites from the ABIDE-II dataset were included to maximize the sample size, and they differ substantially in imaging acquisition protocols, possibly confounding our current findings. In fact, the confounding of site difference is a general issue for all multi-site imaging studies, and completely removing it remains difficult. To minimize this confounding effect, the present study adopted the scheme of previous studies (Hahamy et al., 2015; Valk et al., 2015), as following. First, we applied the same stringent inclusion/exclusion criterion across the four imaging sites, and for each imaging site, the included ASD and TD subjects were well matched, in terms of age, sex, and sample size. Next, the same data processing pipeline was used across the four imaging sites. Finally, we included the “imaging site” as a covariate in statistical models, which should largely remove site confounding effects on final statistical results. However, the three steps may not completely rule out the possibility of the site confounding, and it would be ideal in the future to validate the findings with a large independent dataset from a single imaging site.

Next, the current findings are overlapped with our previous study (Zhong et al., 2017), with both showing rightward asymmetries of hemispheric network efficiencies and a decreased rightward network asymmetry from adolescence to young adulthood in healthy. Given that the two studies differed substantially in participants and imaging protocol, this consistency provided support for the validity of our current findings. In both studies, the same hemispheric network construction method was employed: the 512-ROI random parcellation for node definition and diffusion MRI tractography for edge definition. This random parcellation scheme was adopted to achieve spatially high-resolution networks, which has been repeatedly applied in previous studies (Bai et al., 2012; Crossley et al., 2014; Zalesky et al., 2010). However, this scheme does not respect anatomical and functional (sub-) cortical boundaries, and it is important to perform the same network asymmetry analyses using a neurobiologically guided parcellation in the future. On the other hand, the adopted diffusion MRI tractography method has inherent limitations for handling crossing or kissing fibers, which remains a general challenge in diffusion MRI studies. More advanced imaging and tractography should be developed and applied in the future (Jeurissen et al., 2011; Tournier et al., 2008). In addition, in the present study, the hemispheric networks involve only intra-hemispheric connections and the inter-hemispheric connections (e.g., the corpus callosum) were not taken into account, since we mainly focused on the differences/asymmetry of the two hemispheric networks between two groups. In general, however, the asymmetry of the two hemispheric networks might relate to the inter-hemispheric connections to some extent, which can be exclusively explored in the future.

Finally, while the age range was quite similar for our TD and ASD group, the specific age distribution was not well matched, leading to a trend of mean age difference between the two groups. Future studies with well age-matched groups therefore are highly desired to validate current findings. At last, it is worth noting that current results are based on a cross-sectional dataset and should be interpreted with caution for conclusions regarding the development of efficiency asymmetry. Future studies are encouraged to use a longitudinal design to confirm the developmental trajectory aberration of ASD identified in the present study.

5. Conclusion

The present study revealed an atypical developmental trajectory of hemispheric network asymmetry and aberrant development of the right hemisphere, using a large cohort of ASD patients from childhood to young adulthood. Reduced rightward asymmetry of the network local efficiency was found to be associated with more severely restricted, repetitive behaviors in ASD. These findings provide important insights into the abnormal development of the ASD brain.

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Contributors

Long Wei performed the data analyses and wrote the manuscript draft. Suyu Zhong performed statistical analyses and wrote the manuscript draft. Gaolang Gong and Shengdong Nie designed the study, wrote and reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

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