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Different Developmental Pattern of Brain Activities in ADHD: A Study of Resting-State fMRI

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Keywords

Resting-state functional magnetic resonance imaging (rs-fMRI) · Attention deficit hyperactivity disorder (ADHD) · Brain development · Functional connectivity · Topological property

Abstract

There are distinct symptoms for attention deficit hyperactivity disorder (ADHD) at different ages. To explore the developmental mechanism of ADHD from childhood to adolescence, patients from different age groups with ADHD drawn from a large dataset should be investigated. In this study, we hypothesized that there are significant differences in the developmental patterns of local and global brain activities between ADHD and typically developing (TD) individuals. Three voxel-based measurements and the functional connectivity (FC) of the brain networks were extracted from resting-state functional magnetic resonance imaging (fMRI) of both ADHD and TD participants 7–16 years of age. The topological properties of brain networks in both groups were also analyzed, including hubs, hemispheric symmetry, together with local and global efficiency. The results showed, from the local perspective, that the ADHD group had abnormal amplitude of low-frequency fluctuation, fractional amplitude of low-frequency fluctuation, and regional homogeneity in the medial orbital frontal cortex, anterior cingulate cortex, postcentral gyrus, thalamus, precuneus, and cerebellum compared with the TD group. From the global perspective, the aberrant FC between multiple networks, such as the default mode network (DMN), the attention network, and the executive control network, might directly contribute to symptom differences in childhood and adolescence in ADHD patients. Finally, from the developmental perspective, there was delayed maturation of brain networks in the ADHD group, especially in the DMN. Overall, we presented the differences in brain networks between the ADHD and TD group from multiple perspectives and demonstrated the developmental abnormality of brain networks in ADHD patients, contributing to the study of the etiology of ADHD.

Introduction

Attention deficit hyperactivity disorder (ADHD) is usually considered to be a neurodevelopmental disorder [1], and is mainly characterized by inattention, hyperac-

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tivity, disruptive behavior, and impulsivity [2]. The incidence and symptoms of ADHD show different patterns between age groups. Some meta-regression analyses indicate that the incidence of ADHD is approximately between 5.29 and 7.1% in children and adolescents [3–5]. Several studies have revealed that about 30–50% of people diagnosed with ADHD in childhood keep these symptoms into adolescence or adulthood [6]. In addition, Kooij et al. [3] point out that symptoms of hyperactivity in children tend to go away with age and turn into "inner restlessness" in teens and adults with ADHD. Thus, we speculate that the developmental patterns of regional and global brain activities in ADHD subjects could be significantly different from those in typically developing (TD) subjects.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a method of functional brain imaging based on spontaneous fluctuations in the blood oxygen level-dependent signal to describe the functional architecture of the brain [7]. It is widely used in the study of local and global brain activity [8, 9]. On the one hand, many rs-fMRI studies have applied amplitude of low-frequency fluctuation (ALFF) [10], fractional amplitude of low frequency fluctuation (fALFF) [11], and regional homogeneity (ReHo) [12] into investigating local brain activity in ADHD patients. ALFF reflects the degree of spontaneous activity at each voxel in the light of the level of oxygen content [13]. In order to further eliminate the effects of noise, fALFF calculates the ratio of the power spectrum of the low frequency (0.01–0.08 Hz) to that of the entire frequency range, which improves the sensitivity and specificity when investigating spontaneous brain activities [14]. ReHo characterizes the coherence of neural activity of a specific brain region with its neighboring brain regions [15], i.e., it measures the degree of functional differentiation in certain regions. On the other hand, functional connectivity (FC) analysis, based on graph theory, has an increasingly wide utilization in studies of local and global brain activity, by focusing on how the activation in one brain region relates to other brain regions [16]. Practically, the FC measurement based on whole-brain networks at rest is well-suited for using in both the research and clinical contexts, considering that resting-state data is comparatively straightforward to gather and share across acquisition sites without excessive consideration of linguistic and cultural barriers. Furthermore, in view of the currently available imaging methods and limited informatics capacity, FC at the macroscale level is the most feasible for delineating a first draft of the human brain connectome [17].

Along with previous case-control studies using rs-fMRI imaging, the converging point of these findings supports the surmise that there are extensively dysregulated brain activities in ADHD patients. For example, An et al. [12] compare ALFF and ReHo of 23 medication-naïve boys with ADHD coupled with 25 age-matched controls, and finds that the abnormal brain activity of ADHD patients mainly occurs in fronto-cingulo-occipito-cerebellar areas. In a study on 46 children with ADHD, Shang et al. [18] explore the differential effects of methylphenidate and atomoxetine on intrinsic brain activity, including fALFF and ReHo which are quantified via rs-fMRI at baseline and week 12. For 33 boys with ADHD as well as 32 healthy control subjects, Li et al. [19] calculate ALFF and seed-based FC across subjects, revealing that aberrant ALFF in the ADHD group appears in the globus pallidus, superior frontal gyrus (SFG), and orbital frontal cortex (OFC) compared to healthy controls. Compared with 23 normal controls, Sun et al. [20] discover that the dorsal anterior cingulate cortex (ACC) in 19 drug-naïve boys with ADHD shows a significantly decreased negative FC within the default mode network (DMN), including the dorsomedial prefrontal cortex and the posterior cingulate cortex (PCC).

In summary, it is worth noting that many studies are based on limited samples, which could not depict representative brain activity pattern. Moreover, some measurements used do not combine well with each other, and may not cover all of the local and global brain activity. Finally, yet importantly, there are different abnormal behavioral performances in ADHD patients of different age groups [21], probably related to changes in abnormal brain activities at different ages. We hypothesized that there were significant differences in the developmental patterns of local and global brain activities between an ADHD and a TD group. Furthermore, according to the results of previous studies, we also considered that ADHD patients could exhibit the development retardation of extensive brain networks compared with TD subjects, especially in the DMN.

In this study, a large, rs-fMRI dataset with 266 ADHD subjects and 719 TD subjects from aged 7–16 years was adopted. Firstly, three voxel-based measurements were used in exploring the abnormal local brain activity of ADHD. ALFF, fALFF, and ReHo of each subject were calculated and compared between groups. The functional network of the brain of each group was then constructed, to investigate the differences of resting-state FC patterns in children and adolescents with and without ADHD. The DMN of each group was constructed by a seed-based

Table 1. Sample characteristics

Sites	Field strength	Voxel size, mm	ADHD (n = 266)			TD (n = 719)		
			n	mean age, years	male/female	n	mean age, years	male/female
KKI	1.5 T	3.0 × 3.0 × 3.0	18	9.78	11/7	101	9.70	64/37
NeuroIMAGE	1.5 T	3.5 × 3.5 × 3.0	9	14.67	9/0	3	15.33	0/3
NYU	3 T	3.0 × 3.0 × 4.0	121	10.24	89/32	155	11.41	92/63
OHSU	3 T	3.8 × 3.8 × 3.8	22	8.27	15/7	79	8.96	45/34
Peking	3 T	3.1 × 3.1 × 3.5	93	11.58	81/12	104	10.86	60/44
Pittsburgh	3 T	3.1 × 3.1 × 4.0	3	14.33	2/1	56	12.91	34/22
WashU	3 T	4.0 × 4.0 × 4.0				49	10.29	27/22
Leuven	3 T	3.5 × 3.5 × 4.0				16	14.00	12/4
MaxMun	3 T	3.0 × 3.0 × 4.0				6	11.17	6/0
Olin	3 T	3.4 × 3.4 × 4.0				6	13.83	5/1
Pitt	3 T	3.1 × 3.1 × 4.0				13	12.92	10/3
SDSU	3 T	3.4 × 3.4 × 3.4				16	13.88	11/5
Stanford	3 T	3.1 × 3.1 × 4.5				19	9.47	16/3
Trinity	3 T	3.0 × 3.0 × 3.5				13	13.77	13/0
UCLA	3 T	3.0 × 3.0 × 4.0				42	12.24	36/6
UM	3 T	3.4 × 3.4 × 3.0				14	14.21	13/1
USM	3 T	3.4 × 3.4 × 3.0				13	12.62	13/0
Yale	3 T	3.4 × 3.4 × 4.0				14	12.86	9/5

KKI, Kennedy Krieger Institute; NeuroIMAGE, NeuroIMAGE sample; NYU, New York University Child Study Center; OHSU, Oregon Health & Science University; Peking, Peking University; Pittsburgh, University of Pittsburgh; Leuven, University of Leuven; MaxMun, Ludwig-Maximilian University Munich; Olin, Olin, Institute of Living at Hartford Hospital; Pitt, University of Pittsburgh School of Medicine; SDSU, San Diego State University; Stanford, Stanford University; Trinity, Trinity Centre for Health Sciences; UCLA, University of California, Los Angeles; UM, University of Miami; USM, University of Utah School of Medicine; WashU, Washington University; Yale, Yale Child Study Center.

method, and the groups were compared. Finally, the topological properties of the brain functional network such as the hubs, hemispheric symmetry, and local and global efficiency were calculated and compared, respectively.

Method

Dataset

Data were obtained from the 1000 Functional Connectomes Project (1000-FCP) (http://fcon_1000.projects.nitrc.org/). This is a globally shared neuroimaging database that collects structural and rs-fMRI data from multiple sites. For the ADHD participants, the data were acquired from a multisite ADHD-200 sample, which contains rs-fMRI and structural MRI images of typically developing control participants and participants with a DSM-IV-TR diagnosis of ADHD and with an age of 7–21 years [22]. In order to include more subjects, the data of 438 and 281 TD participants were, respectively, obtained from the ADHD-200 dataset and the Autism Brain Image Date Exchange (ABIDE) sample across multiple independent imaging sites [23]. The TD participants from both databases were specially selected according to the same criteria. For both ADHD and TD subjects, the inclusion criteria included: an age of 7–16 years, no history of neurological disease, and no diagnosis of either schizophrenia or affective disorder, an image covering at least 95% of the brain, and an IQ score >80.

Thirty-one ADHD subjects (20 children and 11 adolescents) and one TD subject (1 child) were excluded from further analysis due to excessive head motion (maximal head motion >2 mm or translation >2° rotation in any direction) or incomplete information. Clinically, ADHD can be classed into three subtypes: combined subtype ADHD (ADHD-C), inattentive subtype ADHD (ADHD-I), and hyperactive/impulsive ADHD (ADHD-H). Data on 266 ADHD subjects (146 ADHD-C, 112 ADHD-I, and 5 ADHD-H) and 719 TD subjects aged 7–16 years were included in the final analysis. To make a thorough inquiry about the developmental differences in brain activities between the ADHD and TD groups, participants were also subdivided into two age groups: childhood, i.e., 7–11 years old (TD n = 407; ADHD n = 169), and adolescence, i.e., 12–16 years old (TD n = 312; ADHD n = 97). Table 1 summarizes the demographic and image acquisition information of these participants.

Image Preprocessing

T1 and rs-fMRI data were preprocessed with the toolkit DPARSF v4.3 [24]. The first 10 volumes were removed due to the magnetization instability in the scanner. All images were corrected

Table 2. Regions showing significant changes in ALFF, fALFF, and ReHo in the ADHD group versus the TD group

ADHD>TD				ADHD<TD			
region	L/R	volume, mm^3	*p* value	region	L/R	volume, mm^3	*p* value
ALFF							
Total							
Supplementary motor area	L	7,101	<0.001	Cerebellum	LR	11,799	<0.001
Medial orbital frontal cortex	L	3,348	<0.001				
Postcentral gyrus	L	2,835	<0.001				
Anterior cingulate cortex	L	2,160	<0.001				
Precuneus	LR	2,160	<0.001				
Precentral gyrus	R	1,998	<0.001				
Cerebellum	LR	1,053	0.002				
Insula	R	675	<0.001				
Thalamus	R	540	<0.001				
Childhood							
Posterior orbital frontal cortex	L	40,284	<0.001	Cerebellum	LR	11,745	<0.001
Putamen	R	8,451	<0.001	Superior parietal cortex	LR	1,107	<0.001
Cerebellum	R	2,430	0.004				
Inferior frontal gyrus	R	1,512	<0.001				
Precentral gyrus	R	1,485	<0.001				
Postcentral gyrus	R	1,485	<0.001				
Caudate	R	1,296	<0.001				
Lingual	R	1,296	<0.001				
Supramarginal gyrus	L	945	<0.001				
Superior occipital cortex	L	567	<0.001				
Insula	L	594	0.004				
Thalamus	L	621	<0.001				
fALFF							
Total							
Middle cingulate cortex	LR	5,373	<0.001	Cerebellum	LR	5,508	<0.001
Anterior cingulate cortex	L	4,590	<0.001	Vermis		4,212	<0.001
Postcentral gyrus	R	3,051	<0.001				
Lingual	LR	1,755	0.002				
Medial orbital frontal cortex	L	1,728	<0.001				
Thalamus	LR	1,026	0.002				
Superior temporal cortex	L	999	0.002				
Precuneus	R	945	0.002				
Insula	R	567	<0.001				
Childhood							
Middle cingulate cortex	LR	2,295	<0.001				
Supplementary motor area	L	2,295	0.001				
Adolescence							
Medial orbital frontal cortex	L	1,215	0.001				

for within-scan acquisition time differences between slices, and then realigned to the middle volume to correct interscan head motions. During the head motion correction procedure, the magnitude of the head motion at each time point for 6 parameters (3 for shift and 3 for rotation) was obtained for each subject. Individuals exhibiting >2 mm maximum translation or 2 mm of angular rotation during the resting-state scan were excluded from further analysis. Images were registered onto the Montreal Neurological Institute standard template, and subsequently resampled to 3 mm of isotropic resolution. Spatial smoothing was applied with a Gaussian kernel of 4 mm full-width at half-maximum (FWHM) to improve the signal-to-noise ratio (SNR). Besides, the mean signal of the white matter and cerebrospinal fluid were removed as covariates. Linear-trend removal coupled with band-pass filtering (0.01–0.1 Hz) were also performed. Finally, ALFF, fALFF, and ReHo of each participant were calculated with REST v1.8 [25].

Table 2 (continued)

ADHD>TD				ADHD<TD			
region	L/R	volume, mm^3	*p* value	region	L/R	volume, mm^3	*p* value
ReHo							
Total							
Caudate	R	11,069	<0.001	Vermis		29,052	<0.001
Anterior cingulate cortex	L	10,962	<0.001	Hippocampus	LR	4,131	<0.001
Supplementary motor area	L	10,962	<0.001	Precuneus	R	3,294	<0.001
Medial superior frontal cortex	L	10,962	<0.001	Inferior temporal gyrus	R	2,052	<0.001
Postcentral gyrus	R	9,639	<0.001	Superior parietal gyrus	L	1,404	<0.001
Medial orbital frontal cortex	R	5,562	<0.001	Superior frontal gyrus	L	1,296	0.001
Middle temporal cortex	R	5,397	0.003	Angular	L	999	<0.001
Inferior frontal gyrus	R	3,348	0.001	Inferior occipital gyrus	L	945	<0.001
Insula	LR	2,727	<0.001	Post cingulate cortex	L	837	<0.001
Putamen	R	1,512	<0.001	Superior frontal cortex	R	621	0.006
Precentral gyrus	L	1,296	0.001	Anterior cingulate cortex	R	621	<0.001
Thalamus	R	1,269	0.001				
Parahippocampal gyrus	R	1,026	<0.001				
Precuneus	L	783	<0.001				
Superior occipital cortex	L	783	0.002				
Childhood							
Anterior cingulate cortex	L	12,690	<0.001	Vermis		33,912	<0.001
Postcentral gyrus	R	9,639	<0.001	Superior parietal gyrus	LR	7,453	<0.001
Insula	LR	7,020	<0.001	Middle occipital gyrus	L	5,438	<0.001
Medial orbital frontal cortex	L	2,268	0.001	Inferior occipital gyrus	L	2,691	<0.001
Superior frontal cortex	LR	2,727	0.004	Supplementary motor area	L	945	<0.001
Middle frontal cortex	LR	1,863	0.001	Inferior temporal gyrus	R	756	<0.001
Superior temporal cortex	R	1,188	<0.001	Angular	L	675	<0.001
Precuneus	LR	1,080	0.001				
Caudate	R	891	0.002				
Adolescence							
Medial orbital frontal cortex	R	3,051	<0.001	Cerebellum	R	810	<0.001
Middle temporal gyrus	L	810	<0.001				
Inferior temporal gyrus	R	540	<0.001				

The Measurement of FC and the Construction of DMN

To better measure the FC between brain regions, the brain was divided into 90 regions of interest (ROIs) by automated anatomical labeling atlas [26]. The average time series of each region was obtained by averaging the time series of all voxels in the region. The correlation between two ROIs was then quantified with Pearson's correlation coefficient of interregional time series. The symmetric correlation matrix (90 × 90) of FC was constructed for each subject. The average correlation matrix of each group was also calculated. As for the construction of DMN, the selected seed regions were located in the bilateral medial SFG (mSFG), bilateral inferior temporal gyrus, bilateral PCC and bilateral precuneus, which constituted a sub-network (4 × 4) of the DMN [27, 28]. The average connection strength of the sub-network plus its standard deviation (SD) was set as the threshold for constructing DMN. Finally, all average correlation matrixes were further thresholded into binary networks where nodes represented brain regions and edges represented undirected connections.

Three Measurements of Topological Properties

In a study of an ADHD and a TD group, Wang et al. [29] verified that the brain functional network of both groups has economical small-world topology. The topological properties of the functional network were represented by three measurements: hubs, local efficiency, and global efficiency. The global efficiency was defined as the inverse of the harmonic mean of the shortest path length between each pair of nodes within the network, which measured the conduction efficiency of information in the whole network [30]. The local efficiency was generated by the average of the efficiency across all sub-networks included in the network [30]. The hubs were depicted as the nodes with the smallest mean shortest path length, or the largest degree (the number of the connections to the node) [31]. In other words, these regions were considered as hubs if their local efficiency was at least 1 SD greater than the average local efficiency of the network. In addition, hemispheric symmetry in both the ADHD and TD groups was regarded as the correlation coefficient be-

tween the corresponding areas in two hemispheres in order to better understand the structural characteristics of the brain network.

Statistical Analysis

The regional brain activity measurements (ALFF, fALFF, and ReHo) in the ADHD and TD groups were compared by a two-sample *t* test on each voxel, taking a significant threshold of $p < 0.01$, with age and gender as covariates, and corrected for multiple comparisons with false discovery rates (FDR). Voxels with $p < 0.01$ and cluster size >540 mm^3 were regarded as showing significant differences between groups. Moreover, the comparison of 3 measurements between two age groups was performed on SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/) with the method above. The differences in the average functional network and DMN between the ADHD and TD groups in the two age groups were presented by BrainNet Viewer v1.53 [32]. Finally, hemispheric symmetry, and local and global efficiency were also performed by two-sample *t* test.

Results

The Differences between the ADHD and TD Groups in Local Brain Activities

On the one hand, the ADHD and TD groups showed significant differences in ALFF, fALFF, and ReHo. When compared with the TD group, these three measurements in the ADHD group exhibited a significant increase in the medial OFC (mOFC), ACC, postcentral gyrus, thalamus, and precuneus, as well as a decrease in the cerebellum. On the other hand, the developmental changes in the ADHD and TD groups regarding these three measurements also showed their own uniqueness. In childhood, the ADHD group showed increased ALFF in the inferior frontal gyrus (IFG), precentral gyrus, and putamen, and decreased ALFF in the superior parietal cortex (SPC) and cerebellum when compared to the TD group, but there were no significant group differences in adolescence. Nevertheless, the ADHD group showed increased fALFF in both age groups, which was only concentrated in small areas such as the middle CC (MCC) and supplementary motor area. As for the ReHo, the ADHD group persistently exhibited it as increasing in the mOFC and decreasing in the cerebellum in both age groups. The group differences in childhood were significantly more extensive than in adolescence. More details are shown in Figure 1 and Table 2.

The Developmental Pattern of FC in the ADHD and TD Groups

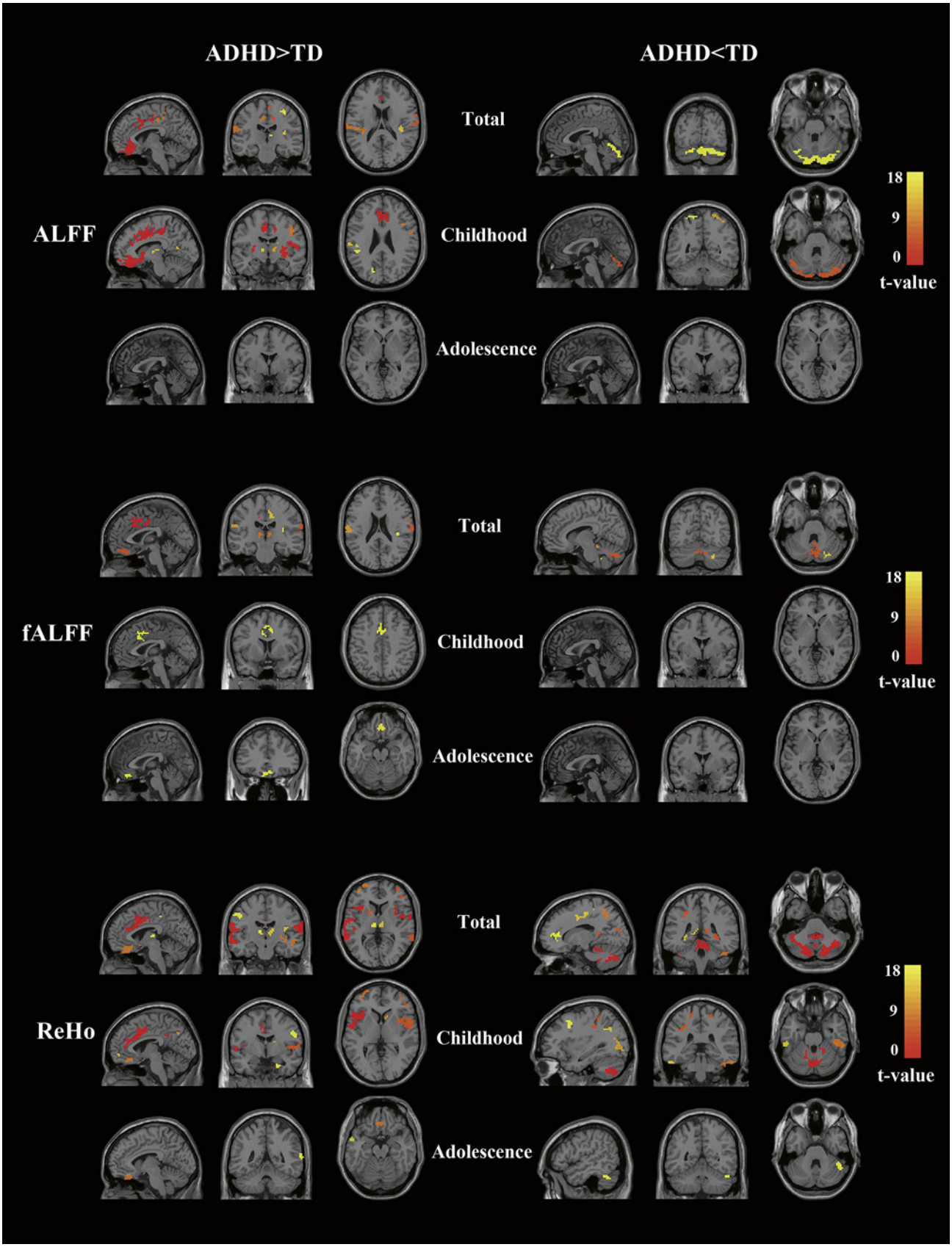
To highlight the most significant connectivity, only the top 2% of the strongest connections within the averaged functional network were selected. As shown in Figure 2a, the developmental pattern of FC in the ADHD and TD group differed. Whether increasing or decreasing with age, for the TD group, most connectivity changes focused on short-range connections such as those between the right mOFC and SFG ($p < 0.002$), the right ACC and SFG ($p < 0.001$), and the left dorsal CC (dCC) and right supplementary motor area ($p < 0.001$), together with a small number of long-range connections such as the connection between the left orbital SFG and PCC ($p < 0.014$). In contrast, during development, the ADHD group exhibited more long-range connections such as those between the left MFG and ITG ($p < 0.002$), the right angular gyrus and dorsal SFG ($p < 0.023$), and the left ACC and dCC ($p < 0.039$), coupled with a small number of short-range connections between the left precuneus and dCC ($p < 0.036$).

The Differences between the ADHD and TD Groups in FC in the Two Age Groups

There were also some differences in FC between the ADHD and TD groups, as shown in Figure 2b. In childhood, there were significantly more functional connections in the ADHD group than in the TD group, such as those between the left middle occipital gyrus (MOG) and lingual gyrus ($p < 0.001$), and between the right MOG and fusiform ($p < 0.001$). The functional connection between the right mOFC and ACC ($p < 0.003$) appeared in the TD group but not in the ADHD group. In adolescence, the ADHD group showed more connections between the right superior temporal gyrus and middle temporal gyrus (MTG) ($p < 0.001$), and fewer connections between the left mSFG and MTG ($p < 0.001$). When compared to the TD group, more long-range connections (e.g., the connection between the right and left IFGs; $p < 0.004$), mostly symmetrical connections between two hemispheres, appeared in the ADHD group. However, the TD group showed more long-range connections within the single hemisphere, such as the connection between the ipsilateral mSFG and MTG ($p < 0.001$).

Fig. 1. The developmental differences in regional brain activity (ALFF, fALFF, ReHo) between the ADHD and TD groups. Total, comparison of all ADHD subjects and all TD subjects; Childhood, comparison of ADHD and TD children 7–11 years of age; Adolescence, comparison of ADHD and TD adolescents 12–16 years of age. Each sub-picture from left to right: sagittal plane, coronal plane, and transverse plane.

(For figure see next page.)



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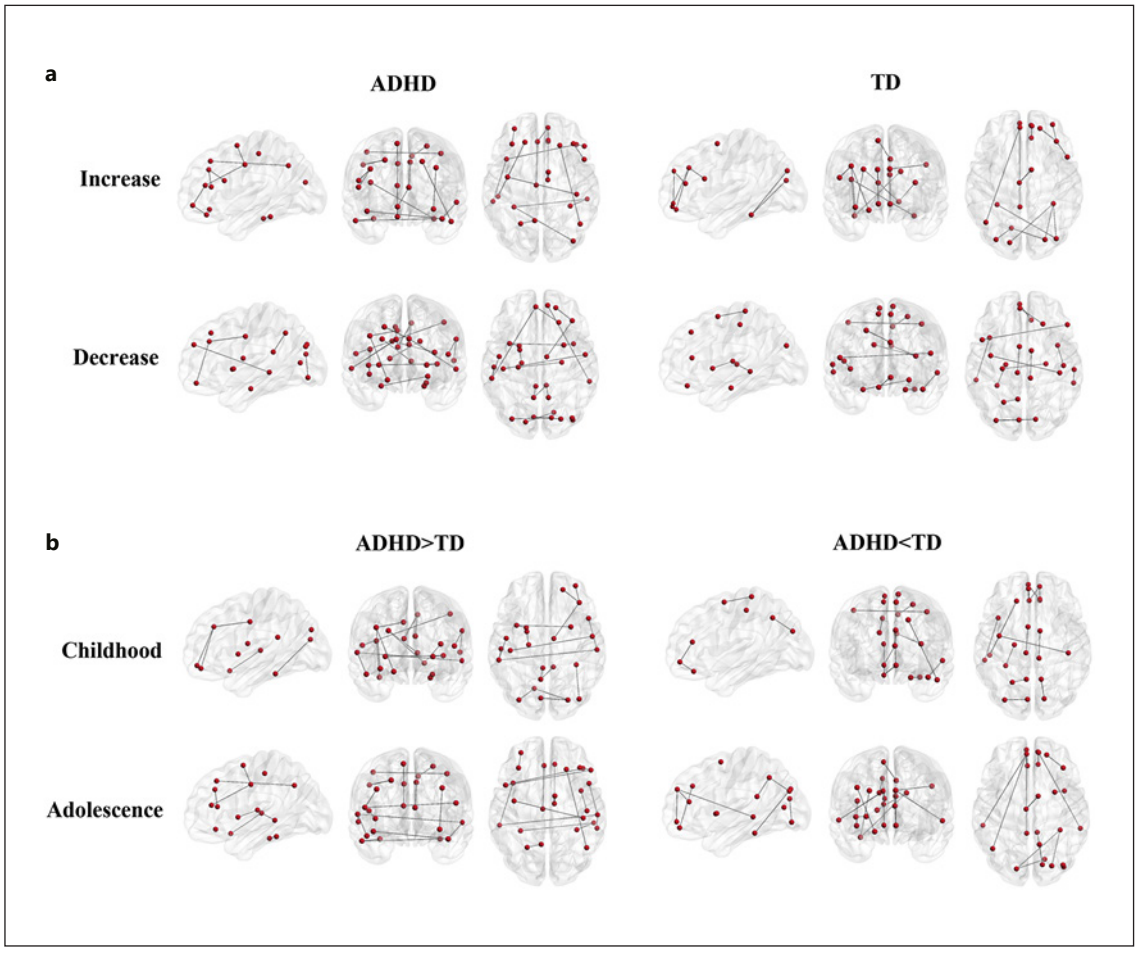

Fig. 2. The developmental changes in the top 2% of average functional connectivity (FC) within the whole-brain network in the ADHD and TD groups, together with their group differences. **a** Developmental pattern differences in FC between the ADHD and TD groups. Increase, increased FC with age; Decrease, decreased FC with age. **b** Differences in FC between the ADHD and TD groups in the two age groups. Each sub-picture from left to right: sagittal plane, coronal plane, and transverse plane.

The Developmental Pattern of DMN in the ADHD and TD Groups

As shown in Figure 3a, the constructed DMN was similar to previous studies [33, 34], which also included the inferior parietal lobule (IPL), the PCC, and the hippocampus except for those known to be seed regions. Although the FC within the DMN decreased with age in both groups, the developmental changes in the ADHD group were more obvious than in the TD group, including connections between the precuneus and hippocampus ($p < 0.001$), the mSFG and hippocampus ($p < 0.001$), and the PCC and hippocampus ($p < 0.001$). For the TD group, there was a small number of decreased connections between the dorsal SFG and middle frontal gyrus (MFG) ($p < 0.034$) with age. Finally, the increased functional connections within the DMN with age were not found in the ADHD or TD groups in the study.

The Differences between the ADHD and TD Groups in DMN in the Two Age Groups

As shown in Figure 3b, in childhood, the ADHD group showed more connections within the DMN than the TD group did, e.g., connections between the ITG and hippocampus ($p < 0.005$), the mSFG and hippocampus ($p < 0.002$), and the precuneus and hippocampus ($p < 0.008$), but there was no obvious difference in adolescence. Nonetheless, compared to the TD group, whether

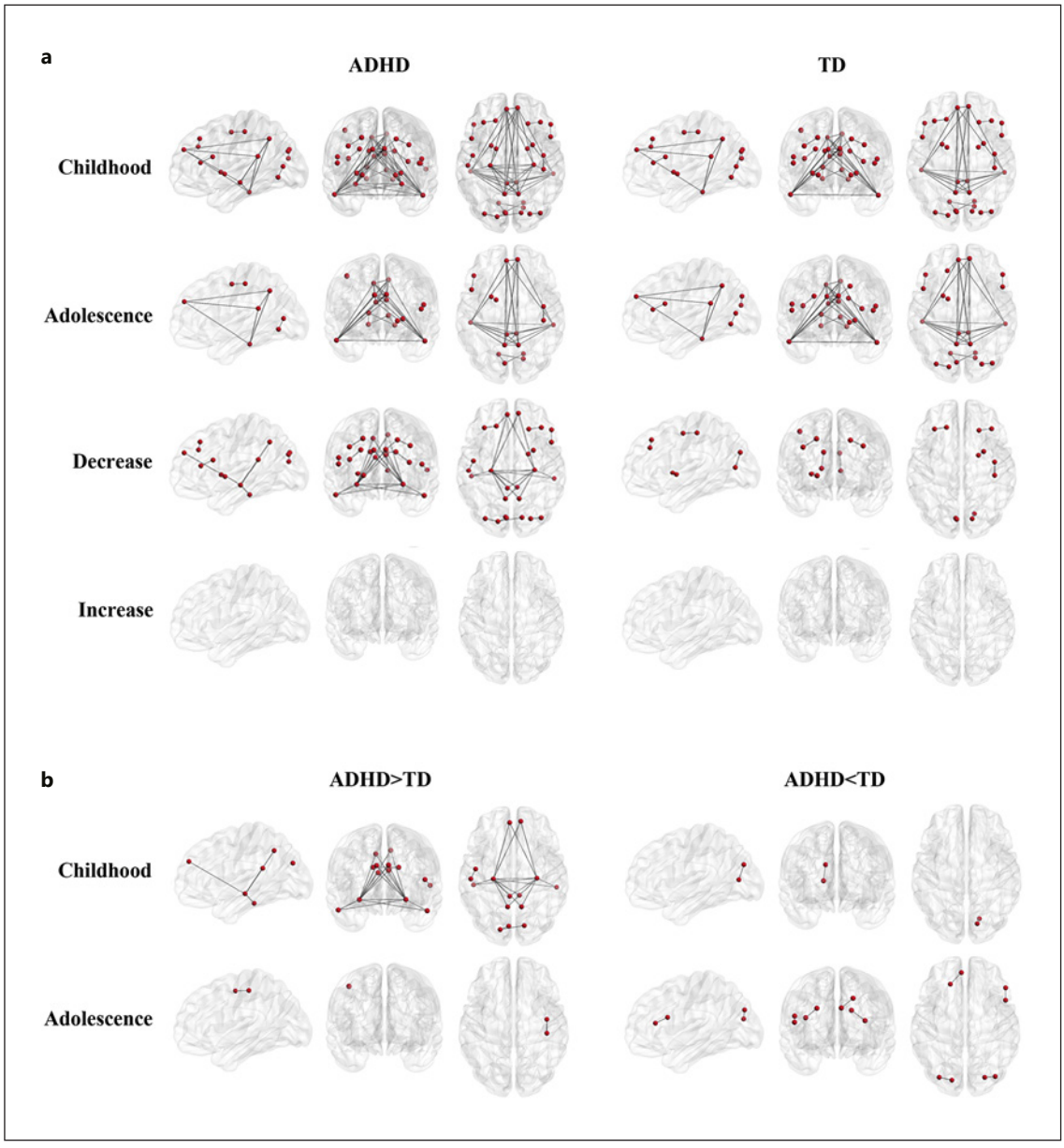

Fig. 3. The DMN of ADHD and TD groups in the two age groups, together with their developmental changes and group differences. **a** The DMN and its developmental changes in the ADHD and TD groups. Increase, increased FC with age; Decrease, decreased FC with age. **b** Differences in DMN between the ADHD and TD groups in the two age groups. Each sub-picture from left to right: sagittal plane, coronal plane, and transverse plane.

in childhood or adolescence, the decreased FC of the DMN in the ADHD group was not obvious. The most significant group differences in FC appeared in childhood and were concentrated on the long-range FC such as the connections between the mSFG and hippocampus ($p < 0.002$) and between the precuneus and hippocampus ($p < 0.008$).

The Developmental Changes in Topology in the ADHD and TD Groups

On the one hand, in both age groups, the hubs of both the ADHD and TD groups persisted in the bilateral temporal gyrus, left precentral gyrus, right SFG, and bilateral MCC and PCC (Fig. 4). On the other hand, more hubs gradually appeared with age, such as in the left SFG, left

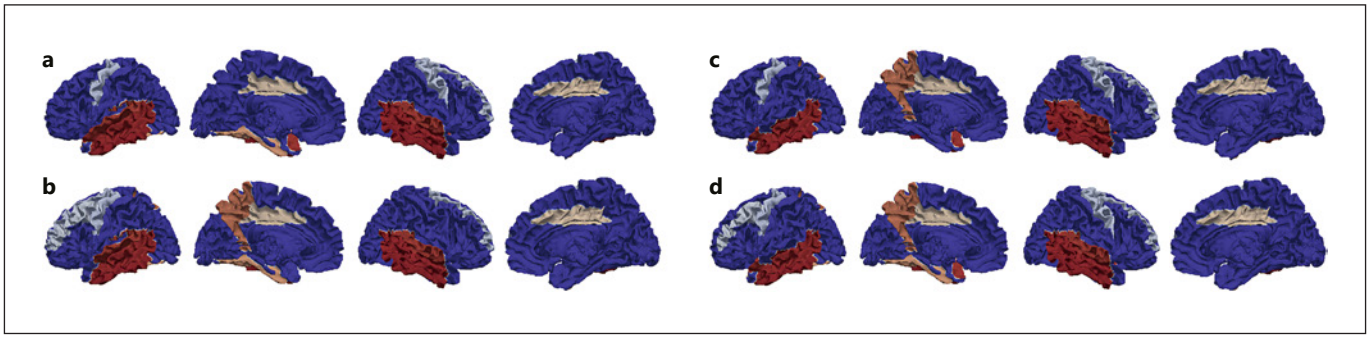

Fig. 4. The developmental changes of hubs in the ADHD and TD groups. Hubs of the ADHD group in childhood (**a**) and adolescence (**b**). Hubs of the TD group in childhood (**c**) and adolescence (**d**). The bright color other than blue indicates hubs. Each sub-picture from left to right: lateral view of the left hemisphere, medial view of the left hemisphere, lateral view of the right hemisphere, and medial view of the right hemisphere.

SPC, and some subcortical tissue (left precuneus). However, there were some differences in hubs between the ADHD and TD groups. For the TD group, the hubs on the left SPC and right precentral gyrus existed throughout childhood and adolescence (Fig. 4c, d). In contrast, the hubs of the ADHD group in the left SPC did not appear until the adolescence, and those in the right precentral gyrus disappeared with age (Fig. 4a, b). Furthermore, we did not observe any significant difference in hemispheric symmetry between the ADHD and TD groups, nor between the two age groups. Between-group differences in local and global efficiency were also not statistically significant.

Discussion

We hypothesized that there would be significant differences between ADHD and TD groups in the developmental pattern of local and global brain activity. We compared local and global brain activity between ADHD and TD groups in childhood and adolescence using 3 voxel-based measurements (ALFF, fALFF, and ReHo) coupled with FC analysis. In addition, we investigated three kinds of topological properties in the brain network in ADHD and TD groups.

From the local perspective, ALFF, fALFF, and ReHo are 3 voxel-based measurements to explore the regional brain activity from different aspects. In our study, when compared to the TD group, the ADHD group showed widespread abnormal regional activity in the frontal cortex, CC, parietal lobe, thalamus, basal ganglia and cerebellum, which mainly involve the attention system [35], and motor and cognitive control circuits [36–38].

From the global perspective, the FC analysis results indicated different developmental patterns between the two groups. For example, the developmental changes in FC in the ADHD group were involved in multiple networks: the frontoparietal, dorsal and ventral attentional, visual, and motor networks, and the DMN [17]. The changes in the TD group were mainly within certain specified regions associated with advanced cognitive function [39].

Previous studies have demonstrated that the abnormal FC (different from that in TD subjects) could be central to the etiology of ADHD [40, 41]. In this study, in childhood, the ADHD group showed more functional connections between the MOG and lingual gyrus and between the MOG and fusiform than the TD group did. These form part of the selective visual attention system [42] (Fig. 2b). This infers that ADHD patients may pay more attention to multiple irrelevant visual stimuli from the environment, even without any attention instruction [43]. Furthermore, whether in childhood or adolescence, the ADHD group exhibited a greater decrease in connectivity in the executive control network than the TD group, e.g., the connection between the SFG and MTG and between the mSFG and ACC, which implied that the abnormal FC within this network could be associated with the symptom of inattention in ADHD patients [44]. Taken together, these results have validated that ADHD patients indeed show a wide range of FC abnormalities (vs. the TD controls).

The DMN has been demonstrated to be the most active during rest, and to deactivate during active task engagement [45]. In this study, there was a similar developmental trend in the ADHD and TD groups, i.e., that part of the FC in the DMN diminished with age. We also ob-

served that the between-group difference within the DMN in childhood tended to disappear in adolescence. This result is in line with a previous study where ADHD participants showed a significant and specific maturational lag in connections within the DMN, evident primarily in its midline core [43].

In the study of the topological properties of the brain network, we found significant group differences and developmental changes only in the hubs. The hub regions have been proven to play a pivotal role in the coordination of information flow within the brain network [46]. During development, brain hubs will gradually shift from primary regions to advanced functioning regions, which means that advanced cognitive function is increasingly strengthened during the development of the human brain [47]. Similar to the results of previous studies, our study revealed that the hubs of both groups were concentrated in the bilateral temporal gyrus, left precentral gyrus, right SFG, and bilateral MCC and PCC [48]. We also observed that the hub regions were more stable in the TD group than in the ADHD group. For example, in the TD group, only the SFG did not appear until adolescence, but in the ADHD group, the changes of hubs with age were more extensive, occurring in the left SPC, right precentral gyrus, and right SFG (Fig. 4). We suggest that the differences in the topological structure of the brain network in the ADHD and TD groups could be linked to underlying dysfunctional neuronal activity [49].

In conclusion, our study exhibited widespread abnormal local and global brain activity of ADHD patients from the developmental perspective, which was primarily concentrated on the attention network, the executive control network, and the DMN. Moreover, compared with the TD controls, ADHD patients showed maturation delay in the DMN, which was further demonstrated by exploring the topology of the brain network in the two groups. To verify whether the unequal number of subjects in the groups affected the results, we also compared all ADHD subjects with the same number of random selected TD subjects, and the test result was very similar to the first. We consider, therefore, that number inequality had no significant impact on our results.

Finally, there are some limitations in the study. First, data were acquired from different institutes, and the different parameter settings could influence the comparative analysis. Second, we only investigated children and adolescents with ADHD, but the study of ADHD adults is also essential. Third, there was only a rough division standard of age groups and a more detailed division may produce different results. Fourth, we did not consider the effect of ADHD subtypes and minor head movements on our results [50, 51]. In the future, the controls regarding independent variables such as IQ, ADHD subtypes, minor head movements, and medication need to be strengthened. Multimodal data, e.g., EEG and DTI data, can also be combined to investigate brain networks from multiple aspects [52]. In short, this study facilitated greater understanding of the developmental pattern of the brain functional network in ADHD patients and the etiology of ADHD.

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Disclosure Statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work and no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, our paper.

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