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ORIGINAL CONTRIBUTION

Abnormal functional network centrality in drug-naïve boys with attention-deficit/hyperactivity disorder

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood and is characterized by inattention, impulsivity, and hyperactivity. Observations of distributed functional abnormalities in ADHD suggest aberrant large-scale brain network connectivity. However, few studies have measured the voxel-wise network centrality of boys with ADHD, which captures the functional relationships of a given voxel within the entire connectivity matrix of the brain. Here, to examine the network patterns characterizing children with ADHD, we recruited 47 boys with ADHD and 21 matched control boys who underwent resting-state functional imaging scanning in a 3.0 T MRI unit. We measured voxel-wise network centrality, indexing local functional relationships across the entire brain connectome, termed degree centrality (DC). Then, we chose the brain regions with altered DC as seeds to examine the remote functional connectivity (FC) of brain regions. We found that boys with ADHD exhibited (1) decreased centrality in the left superior temporal gyrus (STG) and increased centrality in the left superior occipital lobe (SOL) and right inferior parietal lobe (IPL); (2) decreased FC between the STG and the putamen and thalamus, which belong to the cognitive cortico-striatal–thalamic–cortical (CSTC) loop, and increased FC between the STG and medial/superior frontal gyrus within the affective CSTC loop; and (3) decreased connectivity between the SOL and cuneus within the dorsal attention network. Our results demonstrated that patients with ADHD show a connectivity-based pathophysiological process in the cognitive and affective CSTC loops and attention network.

Keywords ADHD · Resting-state fMRI · Degree centrality · Function connectivity

Ming Zhou and Chuang Yang contributed to this study equally.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder in childhood, characterized by inattention, impulsivity, and hyperactivity. This disorder affects 3–10% of school-aged children, with approximately 30–50% of cases persisting into adulthood [1, 2]. Most children are first diagnosed with ADHD when they reach school age, and approximately 75% of those diagnosed are male [3]. There is some debate over the root causes of ADHD, as some biological factors await validation [4]. Neuroimaging biomarkers of ADHD are integral to comprehensive models of ADHD pathophysiology.

Over the past several decades, numerous neuroimaging studies have been conducted to help elucidate the pathophysiology of ADHD. Many resting-state functional connectivity (FC) studies have been conducted in ADHD [5, 6]; various brain networks and widespread intrinsic neural

circuits have been found to be involved in this disorder, such as the fronto-striato-cerebellar network, default mode network (DMN), and executive control network [7]. Typically, resting-state functional connectivity MRI relies upon two main approaches, namely, seed-based and independent component analyses, which focus on the examination of specific brain networks [8, 9]. These approaches do not directly show important functional network topological changes, such as how the whole brain functionally interacts (i.e., connection weights among regions) during the resting state [10].

Degree centrality (DC) is a commonly used graph theory-based measurement of global connectivity. This parameter captures the functional relationships of a given voxel (node) within the entire connectivity matrix of the brain (connectome), rather than with specific nodes or networks [10]. The physiologically meaningful use of DC allows us to map brain hubs with high sensitivity, specificity, and reproducibility [11]. DC analysis has been applied to various mental disorders, such as Alzheimer's disease, major depressive disorder, and schizophrenia [12–14]. Researchers have studied shared and distinct functional network centrality in autism and ADHD children using DC measurements [15]. This study, which included a substantial proportion of female participants, found increases in DC in the basal ganglia. As sex differences in clinical presentations and neuroanatomy of ADHD have been reported [16], we considered this factor and recruited only boys with ADHD in this study.

However, although the DC analysis can identify voxels that showed altered connectivity with other voxels, it cannot provide detailed information regarding the connectivity between a voxel and the particular regions that were changed. Therefore, in the current study, we aimed to detect the specific network centrality alterations in boys with ADHD through a voxel-based analysis of DC. In addition, we further conducted large-scale FC analysis using the regions that showed significant alterations in the local connectivity analysis as seeds. Finally, we performed correlation analyses to detect associations between alterations of cerebral connectivity and ADHD-relevant clinical symptoms.

Methods

Participants

Approval for this study was granted by the local ethics committee of the First Hospital Affiliated with the Wenzhou Medical University. All participants and their parents were fully informed about the purpose and procedures of this study, and written informed consent was obtained from the parents. Patients were recruited from the outpatient population of the First Hospital Affiliated with the Wenzhou Medical University of Mental Health Center. Healthy controls were recruited from local schools. Subjects were interviewed with the Chinese Reversion of Structured Clinical Interview for DSM-IV (SCID-CR), and consensus diagnoses were made using all available information. The following exclusion criteria were applied to all groups: (1) full-scale IQ < 90 based on an age-appropriate Wechsler Intelligence Scale for Children-Chinese Revision; (2) current use or history of psychotropic medication; (3) left-handedness, as assessed with the Annett Hand Preference Questionnaire; and (4) substantial physical illness, or standard MR scanning contraindications. In total, 59 boys with ADHD and 25 healthy controls (HC) were scanned. All participants with ADHD had no history of medication use to treat inattentive symptoms and had no comorbid Axis I disorders. All participants were right-handed Han Chinese.

Behavioral problems were measured using the hyperactivity index from the Chinese revised version of Conners' Parent Rating Scale (CPRS). CPRS is a battery of questions to evaluate problematic behavior across areas such as sleep, temper, and peer relationships, which are aggregated into six factors: conduct problem, study problem, psychosomatic, impulsive–hyperactive, anxiety and hyperactivity index.

Date acquisition and preprocessing

All MRI scans were performed on the GE signal HDx 3.0T MRI scanner with an eight-channel phased-array head coil (GE Medical System, Milwaukee, WI, USA). During the entire scanning procedure, all subjects were in a supine position with their heads snugly fixed by foam pads to reduce head movement. Whole-brain resting-state fMRI (rs-fMRI) data depicting blood oxygen level-dependent (BOLD) signal were obtained using a gradient-echo echo-planar imaging sequence with the following parameters: 31 axial slices, slice thickness = 4 mm, slice gap = 0.2 mm, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, matrix size = 64 × 64; and field of view (FOV) = 192 × 192 mm^2. The rs-fMRI lasted 8 min in total, and 240 volumes were obtained for each participant. To reduce head movement during scanning, we had a general education and practice in the scanner before scanning to ask subjects to relax with their eyes closed without falling asleep and without directed, systematic thought during the process (confirmed by subjects immediately after the experiment). It was confirmed by a subjective report that none of the participants fell asleep during the scan. In addition, we also monitored the head motion when scanning. If the head motion is too severe, we usually stop the process to let the subject have a rest.

Preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF3.2 Basic edition) [17], which synthesizes procedures in statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/

spm) and the resting-state functional MR imaging toolkit V1.8 (REST; http://www.restfmri.net) [18]. For each participant, the first ten volumes were discarded to allow for imaging unit stabilization and subject familiarization, and the remaining images were section-time corrected, realigned to the middle volume, and unwarped to correct for susceptibility-by-movement interaction. Realigned images were spatially normalized to the Montreal Neurological Institute template, and each voxel was resampled to $3 \times 3 \times 3$ mm^3. The normalized images were smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel. Previous work has indicated that normalization of children's MR images to standard adult templates is acceptable for statistical group comparisons [19]. A higher-level Friston-24 model was used to regress head motion effects out of the realigned data (the 24 parameters included 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items). We further calculated the mean frame-wise displacement (FD) as a measure of the micro-scale head motion of each subject. To further reduce the effects of confounding factors, the average signals arising from the ventricles and white matter were removed from the data with linear regression. Linear trend removal and temporal bandpass filtering (0.01–0.08 Hz) were then performed. Head translation movement for all participants was less than 3 mm, and rotation was less than 3°. Mean head motion parameters were tested. Sixteen subjects were excluded because of severe head motion (translation movement was more than 3 mm, or rotation was more than 3°), including 12 ADHD patients and 4 HCs. Finally, 47 boys with ADHD and 21 HCs were included in the study (Table 1). The data on the three-dimensional head motion in each group can be found in Supplementary Table 1.

Table 1 Clinical and demographic characteristic of ADHD patients and HCs

Characteristics	ADHD ($N=47$)	HC ($N=21$)	p
Age	8.51 ± 1.86	9.05 ± 1.80	0.27
Head motion (FD) (mm)	0.21 ± 0.13	0.18 ± 0.10	0.35
Full-scale IQ	115.49 ± 15.78	121.19 ± 11.61	0.14
Conners' Parent Rating Scale			
Conduct problem	1.22 ± 0.54	0.39 ± 0.36	< 0.001
Study problem	1.90 ± 0.72	0.57 ± 0.53	< 0.001
Psychosomatic	0.40 (0,1.4)	0 (0,0.4)	0.016
Impulsive–hyperactive	1.5 (0.5,3)	0.5 (0,1.5)	0.003
Anxiety	0.5 (0,1.5)	0.25 (0,0.75)	0.59
Hyperactivity index	1.56 ± 0.55	0.48 ± 0.39	< 0.001

Values distributed normally or non-normally are presented as mean ± SD or median (minimum, maximum)

Parameters calculation

DC calculation

The DC maps were generated using Pearson correlations in Resting-State fMRI Data Analysis Toolkit software [18]. (http://www.restfmri.net). Specifically, the time course of each voxel within a default mask was extracted and correlated with that of every other voxel within the mask to generate a correlation matrix. After thresholding each correlation at $R > 0.2$, we computed DC as either the sum of connections (binarized) or the sum of the weights of connections (weighted) for each voxel. The resulting voxel-wise DC map was subsequently converted into a z score map by subtracting the global mean DC and dividing by the SD of the whole-brain DC. To determine whether the main results depended on the choice of correlation thresholds, we recomputed the DC maps using other different correlation thresholds (i.e., 0.25, 0.3 and 0.4) and then reperformed statistical analysis.

FC calculation

As reported below, significant DC abnormalities in patients with ADHD (compared with control subjects) were demonstrated in three brain regions (Table 2; Fig. 1), and these three regions (left superior occipital lobe, peak voxel coordinate: − 36 − 81 24; right inferior parietal lobe, peak coordinate: 48 − 39 36; left superior temporal gyrus, peak coordinate: − 48 − 12 − 3) were used as seeds for FC analysis. After bandpass filtering (0.01–0.08 Hz) and linear trend removal, a reference time series for each seed was extracted by averaging the resting-state functional MR imaging time series of voxels within each seed. The time series of each region was averaged and correlated with that of every other voxel. Correlation coefficients between the seed and every other voxel were then converted using the Fisher r-to-z transformation, yielding variants that were approximately normally distributed.

Table 2 Brain regions with significant differences in DC maps between ADHD patients and HCs

Brain regions	MNI (peak voxel)			Cluster size	Peak t value
	X	Y	Z		
Left superior occipital lobe	− 36	− 81	24	117	4.28
Right inferior parietal lobe/supramarginal gyrus	48	− 39	36	90	4.13
Left superior temporal gyrus	− 48	− 12	− 3	52	− 4.55

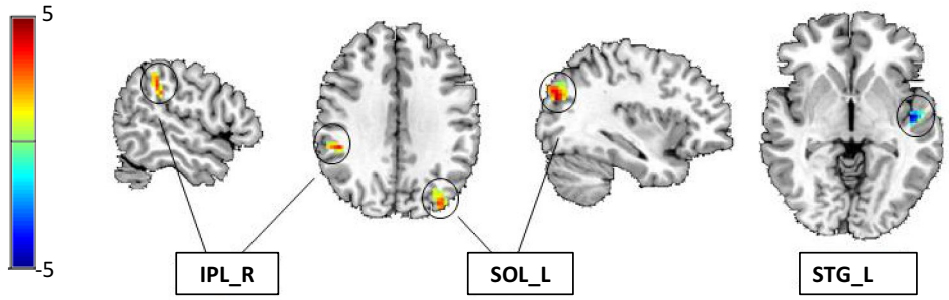

Fig. 1 Group differences of weighted DC maps between patients with ADHD and HCs ($p < 0.05$; AlphaSim-corrected). Patients with ADHD showed significantly increased values (red color) in the left SOL and right IPL and decreased values (blue color) in the left STG. The color scale denotes the *t* value. *SOL* superior occipital lobe, *IPL* inferior parietal lobe, *STG* superior temporal gyrus, *DC* degree centrality, *L* left, *R* right

Statistical analysis

Clinical measures

SPSS 16.0 (SPSS, Inc, Chiago, IL, USA) was used to conduct the statistical analysis. Kolmogorov–Smirnovb test was performed to test normality of the demographic and clinical variables. For the normally distributed variables, the two-tailed independent samples *t* tests were used. Non-normally distributed data were evaluated using the Mann–Whitney *U* test. The significant level was set as $p < 0.05$.

DC analysis

To explore the difference in voxel-wise network centrality between boys with ADHD and the control group, two-sample *t* tests were conducted in a voxel-wise manner in REST software, with age and head motion as covariates. The results were corrected for multiple comparisons to a significance level of $p < 0.05$ by the AlphaSim correction at the cluster level combined with an individual voxel threshold of $p < 0.005$. The peak voxel coordinates with the highest significance within the brain areas of altered DC were described in terms of standard Montreal Neurological Institute coordinates.

FC analysis

After the DC analysis, altered regions in ADHD ($R > 0.2$) were selected as seeds (left superior occipital lobe, peak voxel coordinate: − 36 − 81 24; right inferior parietal lobe, peak coordinate: 48 − 39 36; left STG, peak coordinate: − 48 − 12 − 3) to further explore the difference in FC between the ADHD group and the control group. A two-sample *t* test was used to investigate whether there was abnormal seed-based functional connection in ADHD patients compared with the control group. The results were corrected for multiple comparisons to a significance level of $p < 0.05$ by the AlphaSim correction at the cluster level combined with an individual voxel threshold of $p < 0.001$. The peak voxel coordinates with the highest significance within the brain areas of altered FC were described in terms of standard Montreal Neurological Institute coordinates.

Correlation analysis

In the ADHD group, two-tailed Pearson correlation analyses were performed in software (SPSS 16.0; SPSS) to assess the relationship between the characteristics of behavioral problems and averaged eigenvalues of altered DC and FC extracted using the eigenvariate option in SPM8.

Results

Participant characteristics

In total, 21 male controls and 47 boys with ADHD were included in the study (Table 1). No significant difference was found in age ($p = 0.27$), handedness (all right-handed), head motion ($p = 0.35$), and IQ ($p = 0.14$) between the two groups. As expected, patients with ADHD showed higher scores in conduct problems ($p < 0.001$), study problems ($p < 0.001$), psychosomatic ($p = 0.016$), and impulsive–hyperactive ($p = 0.003$) and hyperactivity index ($p < 0.001$) from the CPRS, indicating more severe behavioral problems. Values distributed normally or non-normally are presented as mean ± SD or median (minimum, maximum).

DC analysis

Due to the highly consistent results of the weighted and binarized measurements, the present findings are primarily based on the weighted maps. After thresholding each correlation

at $R > 0.2$, patients with ADHD exhibited decreased DC in the left superior temporal gyrus (STG) and increased DC in the left superior occipital lobe (SOL) and right inferior parietal lobe (IPL)/supramarginal gyrus (Fig. 1; Table 2). In addition, we obtained similar results with different thresholds ($R > 0.25$, $R > 0.3$ and $R > 0.4$) except for the change in significance in the left STG (see Supplementary Table 2).

FC analysis

For the group comparison, in subjects with ADHD (relative to controls), the left STG showed increases in FC with the superior/medial frontal gyrus (SFG), orbitofrontal cortex (OFC) and lingual gyrus (LG) and decreases in FC with right thalamus and bilateral putamen. In addition, decreased connectivity was observed between the left SOL and cuneus (Figs. 2, 3, Table 3). We did not find any significance when the seed was right IPL.

Correlation analysis

No significant correlations were found when considering Pearson correlation analyses between the characteristics of behavioral problems and averaged eigenvalues of altered DC and FC for the ADHD group with a threshold of $p < 0.05$.

Discussion

In this study, we sought to examine the whole-brain intrinsic functional architecture with both DC and FC methods in drug-naïve boys with ADHD. We found that boys with ADHD exhibited (1) decreased centrality in the left STG and increased centrality in the left SOL and right IPL; (2) decreased FC between STG and putamen and thalamus, which belong to the cognitive CSTC loop and increased FC between the STG and medial/superior frontal gyrus within the affective CSTC loop [20, 21]; and (3) decreased connectivity between SOL and cuneus within the dorsal attention network.

The IPL abnormality in ADHD is not surprising, given previous evidence highlighting functional local or connection alterations in this region for ADHD [22, 23]. The finding of a higher degree of IPL in ADHD children is indicative of more areas showing correlated activity in this region [24], which is coincident with the frequent observation of elevated metabolism of this region in PET studies during the resting state [25]. As a core hub of DMN, ILP has been well studied in ADHD [9, 26]. In the present study, the increased network centrality of IPL is consistent with some task-related fMRI studies, which showed a lack of DMN suppression and increased network connectivity in ADHD patients [27, 28]. The inferior parietal regions have been proposed to be the neuroanatomical substrates of top-down processes of

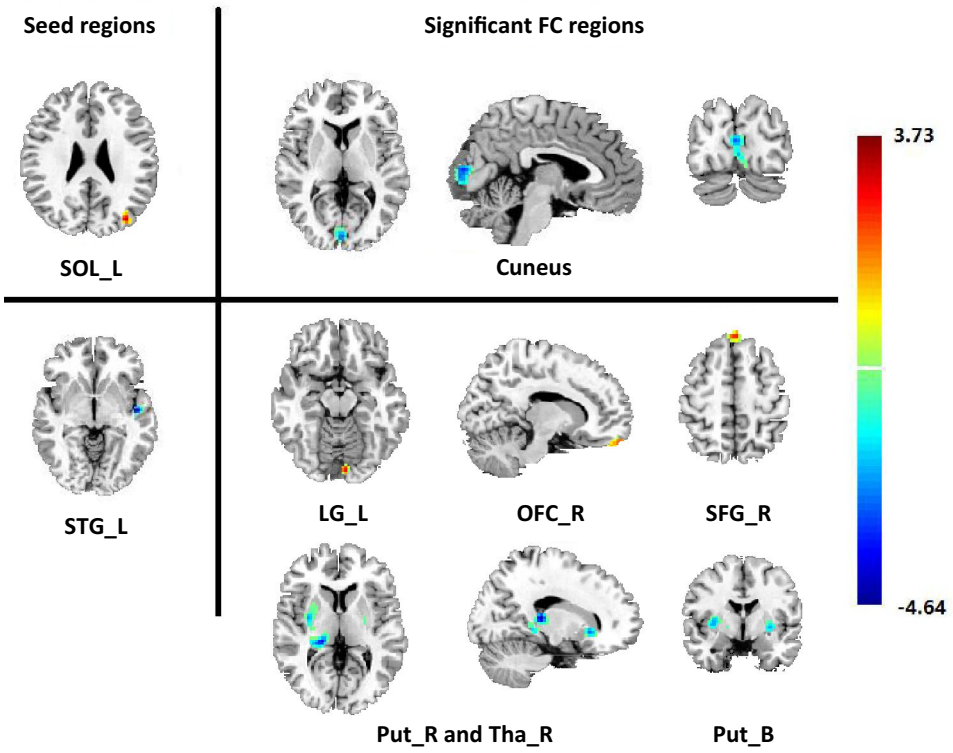

Fig. 2 Group differences of seed-based FC analysis between patients with ADHD and HCs ($p < 0.05$; AlphaSim-corrected). The first column shows the seed regions. There is no difference for FC maps with the seed of right IPL. The red color represents increased FC with seed, while the blue color shows decreased FC. *STG_L* left superior temporal gyrus, *LG_L* left lingual gyrus, *Tha_R* right thalamus, *Put_R* right putamen, *Put_B* bilateral putamen, *OFC_R* right orbitofrontal cortex, *SFG_R* right superior frontal gyrus, *SOL_L* left superior occipital lobe

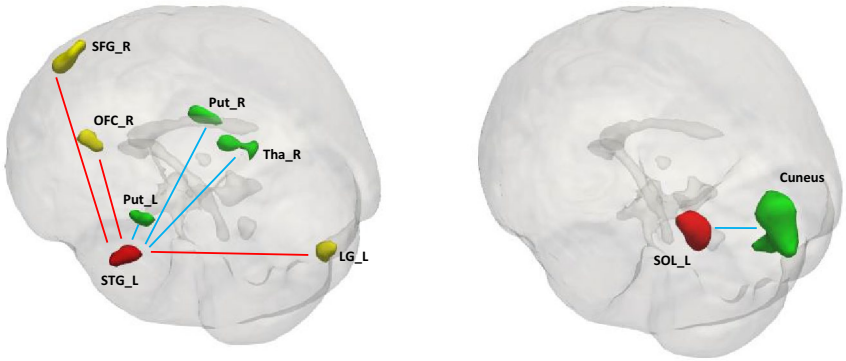

Fig. 3 Anatomic representations show differences in FC between patients with ADHD and healthy control subjects. The red nodes represent the seed areas of FC. The yellow nodes and red lines represent increased FC in patients with ADHD relative to healthy control subjects; the green nodes and blue lines represent decreased FC in patients with ADHD relative to healthy control subjects. *STG_L* left superior temporal gyrus, *LG_L* left lingual gyrus, *Tha_R* right thalamus, *Put_R* right putamen, *Put_L* left putamen, *OFC_R* right orbitofrontal cortex, *SFG_R* right superior frontal gyrus, *SOL_L* left superior occipital lobe

Table 3 Significant differences in FC between ADHD patients and HCs

Seed area	Area with altered functional connectivity	Peak *t* value	MNI (peak voxel)			Cluster size
			x	*y*	*z*	
Left superior occipital lobe	Cuneus	− 4.64	0	− 93	0	108
Right inferior parietal lobe/ supramarginal gyrus	No significant result					
Left superior temporal gyrus	Right putamen and right thalamus	− 5.17	18	− 30	9	398
	Orbitofrontal cortex	4.73	18	48	− 24	30
	Lingual gyrus	4.69	− 6	− 87	− 18	27
	Left putamen	− 4.40	− 30	− 12	0	67
	Superior frontal gyrus	4.39	6	54	48	101

attention [29, 30], suggesting that the dysfunction of this region may be associated with attention deficits in ADHD children.

Furthermore, we found abnormalities ascribable to ADHD within the left STG, right thalamus, and bilateral putamen, as well as in the OFC and medial/superior frontal gyrus (medial/dorsolateral prefrontal cortex), which indicate a core pathway of CSTC loops. CSTC loops are a series of parallel neural circuits that project from the cortex to the striatum and thalamus and then back to the cortex again [31, 32]. In our study, relative to healthy controls, boys with ADHD showed altered FC among several brain regions, including STG, OFC, striatum (putamen), and thalamus and medial/superior frontal gyrus (medial/dorsolateral prefrontal cortex), which are believed to be involved in cognitive and limbic (or affective) loops of CSTC [33–35]. Multiple lines of evidence, including human neuroimaging studies and studies of animal models, suggest that impulsivity involves functional and anatomical abnormalities within the CSTC loops, particularly the cognitive and limbic (or affective) CSTC loops [36, 37]. We found decreased FC in the ADHD group between STG and putamen and thalamus, which are regions within the cognitive CSTC loop, indicating that neurocognitive deficits may reside in the neural substrates underlying executive functions (such as the cognitive CSTC loop) [38]. Increased FC between the STG and medial/superior frontal gyrus (medial/dorsolateral prefrontal cortex), regions within the limbic CSTC, was also found in the present study in ADHD patients. Because the prefrontal regions are associated with the modulation of motor and affective output [39], affective network hyperconnectivity might be related to emotional problems in ADHD. As the significant difference of DC in left STG in ADHD is lost while using higher threshold, we speculate that the correlations between left STG and other brain regions are relatively weak so we can not detect the correlations when using more restricted threshold [10].

The involvement of the left SOL in the visual cortex highlights a region that tends to be overlooked in ADHD studies [40]. While using DC, we have located brain regions showing abnormal functional connectivity; the features of these connections remain unclear [10]. Our finding of increased DC in the occipital cortex indicates an increased number of areas showing correlated activity in this region in ADHD [24]. In addition, the reduced FC between SOL and cuneus may represent inhibitory connections within dorsal attention that preserve network stability by preventing runaway excitation [41]. A previous SPECT study demonstrated local hyperperfusion in the occipital cortex in ADHD in the resting state [42], while other neuroimaging studies showed reduced FC between the occipital lobe and cortical or subcortical regions [43, 44]. The occipital cortex interacts with the dorsal attention network to maintain attention and to suppress attention to irrelevant stimuli [45]. Our findings of disconnection within the occipital cortex further support the relevance of posterior brain areas in the pathophysiology of inattentive symptoms in ADHD [40].

As far as we know, our study is the first to explore ADHD network property through this combination of regional and large-scale network characteristic analysis. We recruited only male ADHD children to exclude the gender confounding, since there was significant difference in clinical manifestation of ADHD boys and girls [3]. In the current study, we found that boys with ADHD exhibited decreased centrality in the left STG and increased centrality in the left SOL and right IPL, which is inconsistent with a previous study comparing ADHD and HC using degree centrality [15]. We boldly speculate that the inconsistency may partly arise from the sex-/gender-based brain differences in ADHD [46]. Gender-specific differences in gray matter volume [46] and surface area [47] have been reported between boys and girls with ADHD. Consistent with our study, previous fMRI study demonstrated reduced activation in a network of brain regions in males with ADHD including prefrontal regions and subcortical regions [48]. Replications of the present findings await future studies accounting for these varied issues in methodology.

Despite the strengths of combining both degree of centrality and functional connectivity analysis to examine the whole-brain intrinsic functional architecture, a reasonable sample size of ADHD with no comorbidity, as well as child population with pure male participants to minimize the confounding effects of sex, the present study still had two limitations. First, sample restriction to all drug-naïve boys enhances the homogeneity but limits the generalizability of our results to adult patients and females with the disorder. Second, there were no significant correlations found between imaging variables and clinical measures, which might be attributed to the relatively small sample size. Further fMRI studies in a larger sample will be needed to reflect brain function of specific areas in ADHD and to examine the relationship between imaging variables and psychological data.

Conclusion

In conclusion, this study applied a data-driven, unbiased search for brain regions displaying network alterations. We found that boys with ADHD exhibited decreased local connectivity in the left STG and increased connectivity in the left SOL and right IPL. On a large scale, disrupted FC within the cognitive and affective CSTC loops and attention network was found in boys with ADHD.

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Author contributions XH and CY conceived and designed the experiments. CY, YL, HL, and HC recruited the patients and collected the data. MZ, XB, and YL performed the data analyses. MZ, CY, XB, and XH wrote the manuscript. HL, XH, and HC helped perform the analysis with constructive discussions. MZ and CY contributed to this study equally.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical statements Approval for this study was granted by the local ethical committee of the First Hospital Affiliated to Wenzhou Medical University. All participants and their parents were fully informed about the purpose and procedures of this study and written informed consent was obtained from the parents.

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