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·Original Article·

Local synchronization and amplitude of the fluctuation of spontaneous brain activity in attention-deficit/hyperactivity disorder: a resting-state fMRI study

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ABSTRACT

Regional homogeneity (ReHo) and the amplitude of low-frequency fluctuation (ALFF) are two approaches to depicting different regional characteristics of resting-state functional magnetic resonance imaging (RS-fMRI) data. Whether they can complementarily reveal brain regional functional abnormalities in attention-deficit/hyperactivity disorder (ADHD) remains unknown. In this study, we applied ReHo and ALFF to 23 medication-naïve boys diagnosed with ADHD and 25 age-matched healthy male controls using whole-brain voxel-wise analysis. Correlation analyses were conducted in the ADHD group to investigate the relationship between the regional spontaneous brain activity measured by the two approaches and the clinical symptoms of ADHD. We found that the ReHo method showed widely-distributed differences between the two groups in the fronto-cingulo-occipito-cerebellar circuitry, while the ALFF method showed a difference only in the right occipital area. When a larger smoothing kernel and a more lenient threshold were used for ALFF, more overlapped regions were found between ALFF and ReHo, and ALFF even found some new regions with group differences. The ADHD symptom scores were correlated with the ReHo values in the right cerebellum, dorsal anterior cingulate cortex and left lingual gyrus in the ADHD group, while no correlation was detected between ALFF and ADHD symptoms. In conclusion, ReHo may be more sensitive to regional abnormalities, at least in boys with ADHD, than ALFF. And ALFF may be complementary to ReHo in measuring local spontaneous activity. Combination of the two may yield a more comprehensive pathophy-siological framework for ADHD.

Keywords: resting state; functional magnetic resonance imaging; regional homogeneity; amplitude of low-frequency fluctuation; attention-deficit/hyperactivity disorder

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurobehavioral disorders in childhood, characterized by symptoms of inappropriate inattention, impulsivity, and hyperactivity. Its underlying psychopathophysiology remains unclear, although convergent anatomical and functional abnormalities have been shown in the fronto-striato-cerebellar circuits[1].

Resting-state functional magnetic resonance imaging (RS-fMRI) has attracted increasing attention since the seminal finding that the low-frequency (0.01–0.08 Hz) fluctuations (LFFs) of the RS-fMRI signal are physiologically important[2]. Most RS-fMRI studies have investigated LFFs from the perspective of temporal correlation or synchronization between distinct brain areas, i.e. functional connectivity, rather than from the perspective of regional activity. Although abnormalities in functional connectivity can reveal the comprehensive and integrative characteristics of two remote brain areas, they cannot tell us which area is more responsible for the observed abnormality in connectivity.

Regional homogeneity (ReHo) and the amplitude of LFF (ALFF) are two approaches to RS-fMRI analysis. ReHo measures the temporal similarity or synchronization of LFFs in neighboring voxels based on the hypothesis that the LFFs in a functional cluster should be highly synchronous[3]. Studies in patients with epilepsy reveal regions exhibiting increased ReHo, in line with the hypothesis of increased local synchronization of epileptic discharges[4, 5]. ALFF measures the amplitude of fluctuation of individual voxels[6]. It has been used to differentiate two resting conditions[7] and differentiate patients with epilepsy from normal controls[8]. During the resting state, regions exhibiting higher ReHo[3] and ALFF[6, 7] than other regions are in line with the location of the default mode network and have the highest metabolic rate as measured by positron emission tomography. These two methods have already been used to explore the functional abnormalities in many brain disorders such as Alzheimer's disease[9, 10] and schizophrenia[11, 12]. Of note, both ReHo and ALFF have been used in ADHD studies. Cao *et al.*[13] used a ReHo approach with 29 ADHD boys and 27 matched controls and found that the ADHD group exhibited decreased ReHo in the fronto-striato-cerebellar circuit and increased ReHo mainly in the occipital cortex, relative to the controls. Using ALFF on a smaller sample, Zang *et al.*[6] from the same research group found that, compared to controls (n = 12), boys with ADHD (n = 13) showed decreased ALFF in fronto-cerebellar regions as well as increased ALFF in more widely-distributed areas including the anterior cingulate cortex (ACC), sensorimotor cortex, temporal cortex, and brainstem. It seems that the ReHo and ALFF results of the two studies are complementary. However, there is no study applying the two methods to the same dataset to explore which is more sensitive to local abnormality and to what extent they can detect different abnormalities.

Here, we used both the ReHo and ALFF approaches to explore the abnormalities of regional brain activity in a more purified sample of 23 medication-naïve ADHD boys and 25 matched healthy controls, and determined whether these functional abnormalities were associated with the symptoms of ADHD. Given the inherent difference in the algorithm between ReHo and ALFF and based on the results of previous ReHo and ALFF studies, we hypothesized that the abnormal patterns of regional spontaneous neural activity in ADHD found by these two approaches may be complementary.

PARTICIPANTS AND METHODS

Participants

Twenty-three stimulant-naïve boys diagnosed with ADHD and 25 age-matched healthy male controls, aged between 11 and 16 years, were included in this study. The data used were part of the dataset analyzed by Cao *et al.*[13], partly overlapped with the datasets analyzed by Zang *et al.*[6] and Tian *et al.*[14], and were the same as the dataset of Cao *et al.*[15]. Patients were recruited from the Outpatients Department of Peking University Institute of Mental Health, while the controls were recruited from nearby schools.

All participants were right-handed. Exclusion criteria for the ADHD group (see Cao *et al.*[15]) were: (1) co-morbidity with other psychiatric disorders, except for conduct disorder or oppositional defiant disorder; (2) neurological abnormalities and other severe diseases; (3) full-scale intelligence quotient (IQ) <80 as measured by the Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R)[16]; or (4) previous treatment with stimulants.

ADHD diagnosis was determined *via* a structured diagnostic interview, the Clinical Diagnostic Interviewing Scale (CDIS)[17], which is based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Scores on the ADHD Rating Scale-IV (ADHD RS-IV)[18] were reported by the parents of both groups; this scale contains all the ADHD symptoms of inattention and hyperactivity/impulsivity according to DSM-IV.

The final statistical analyses were based on the data from 19 patients and 23 controls. Among the 19 patients, five had oppositional defiant disorder and two had conduct disorder co-morbid with ADHD; 12 met the criteria for the predominantly inattentive subtype and the other seven met the criteria for the combined (inattentive/hyperactive-impulsive) subtype.

This study was approved by the Research Ethics Review Board of Peking University Institute of Mental Health. After a detailed explanation of the study procedures, written informed consent was obtained from parents or guardians of the subjects, and all the children agreed to participate.

Data Acquisition

Images were acquired on a Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany) at the Institute of Biophysics, Chinese Academy of Sciences. All participants underwent a resting-state fMRI scan without a specific cognitive task[2], during which they were asked simply to close their eyes, remain motionless as far as possible, not fall asleep, and think of nothing systematically.

The RS-fMRI images were acquired using an echo-planar imaging (EPI) sequence with 30 axial slices: echo time (TE), 30 ms; repetition time (TR), 2 000 ms; flip angle, 90°; field of view (FOV), 220 × 220 mm^2; slice thickness, 4.5 mm; slice skip, 0 mm; matrix, 64 × 64; 240 volumes.

A high-resolution T1-weighted 3D sagittal structural image was also acquired from each participant using a spoiled gradient-recalled sequence providing complete brain coverage. The 3D images were used for spatial normalization in the preprocessing step. Four kinds of parameters for the structural image were involved in the final data (42 participants), because some sequence modifications had been made during the two-year collection period. Briefly, 192 slices were acquired from 20 participants with TE, 3.67 ms; TR, 2 000 ms; flip angle, 12°; inversion time, 1 100 ms; FOV, 240 × 240 mm^2; matrix, 256 × 256. And 176 slices were acquired from another 20 participants with TE, 3.92 ms; TR, 1 770 ms; flip angle, 12°; inversion time, 1 100 ms; FOV, 256 × 256 mm; matrix, 512 × 512. Another two sets of parameters (see[15] for details) were used for the remaining two individuals.

Other scanning sessions were not related to the present study and are not described here.

Data Analysis

The first 10 volumes of individual functional time-series were removed for signal stabilization and the adaptation of participants to the scanner. Image preprocessing (slice timing, head-motion correction, within-subject registration, spatial normalization (voxel size 3 × 3 × 3 mm^3) and smoothing) was performed using the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm). Six participants (four from the ADHD group and two from the control group) with head motion >3 mm translation or >3° rotation in any direction were excluded from further analysis. Spatial smoothing was performed with a Gaussian kernel of 6 mm full-width at half-maximum (FWHM) before ALFF calculation but after ReHo calculation, as smoothing before ReHo calculation greatly increases the regional similarity[19]. Resting-State fMRI Data Analysis Toolkit (REST)[20] was used for the subsequent steps, including linear trend removal and band-pass filtering (0.01–0.08 Hz).

Individual ReHo maps were generated by calculating the Kendall coefficient of concordance (KCC) of the filtered time-series of a given voxel with those of its nearest neighbors (26 voxels) in a voxel-wise manner[3, 21]. Afterwards a whole-brain mask (70831 voxels; made from the Montreal Neurological Institute template) was used to remove the non-brain tissues. For standardization, the individual ReHo maps were divided by their own global mean KCC within the whole-brain mask. Then spatial smoothing was performed on the standardized individual ReHo maps with a Gaussian kernel of 6 mm FWHM.

Individual ALFF maps were calculated as described previously[6]. The filtered time-courses were transformed into the frequency domain by a fast Fourier transform, so the power spectrum was acquired. As the power at a given frequency is proportional to the square of the amplitude of this frequency component, the square root at each frequency of the power spectrum was computed and then the mean square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. The individual ALFF maps were also divided by their own mean ALFF value within the whole-brain mask for standardization.

Statistics

Case-control differences in age and full-scale IQ were analyzed using two-sample *t*-tests in SPSS 13.0. Two-sample *t*-tests were conducted on ReHo and ALFF maps respectively, to determine the group differences using SPM5. Voxels with P <0.01 and cluster size >1080 mm^3 (40 voxels), which resulted in a corrected threshold of P <0.05 determined by AlphaSim in AFNI (FWHM = 6 mm; cluster connection radius = 5 mm; http://afni.nih.gov/afni/docpdf/AlphaSim.pdf), were regarded as showing a significant difference. We defined spherical regions of interest (ROIs) with a radius of 3 mm, centered on the peak voxel of each cluster showing a significant group difference in ReHo and ALFF (nine ROIs of ReHo and one ROI of ALFF). Pearson correlation analyses were then conducted between the ADHD RS-IV score and RS-fMRI measurements (mean ReHo and ALFF) of each ROI in the ADHD group to investigate the relationship between the regional spontaneous brain activity measured by the two approaches and the clinical symptoms of ADHD.

RESULTS

The ADHD and control groups did not differ in age (t = 0.22, P = 0.83), but the IQ of the controls was higher than that of the boys with ADHD (t = −2.98, P = 0.005). As expected, the ADHD RS-IV scores of ADHD boys reported by parents were markedly higher than those of controls (t = 8.43, P < 0.001) (Table 1).

Compared to the controls, the ADHD group showed decreased ReHo in the bilateral cerebellum, right middle frontal gyrus (MFG), right precuneus and bilateral ventral medial prefrontal cortex (vMPFC), and showed increased ReHo in the right dorsal ACC (dACC) and bilateral lingual and fusiform gyri (Table 2, Fig. 1A). But for ALFF, only one cluster in the right occipital cortex exhibited a higher value in the ADHD than in the control group, which was almost completely included in the group-difference map generated by the ReHo approach (Table 2 and Fig. 1B). No clusters showed lower ALFF in the ADHD boys than in the controls.

Among the nine ROIs of ReHo, the ReHo value of that in the right cerebellum (coordinates of the peak voxel: 30, −75, −24) was negatively correlated with the ADHD RS-IV score in the ADHD group (r = −0.66, P = 0.003, Fig. 2A). The ReHo of the ROI in the right dACC (coordinates of the peak voxel: 15, 42, 21) and left lingual gyrus (coordinates of the peak voxel: −24, −60, −6) showed a positive correlation with the ADHD RS-IV score (dACC: r = 0.73, P = 0.001, lingual gyrus: r = 0.55, P = 0.02; Fig. 2B, C). No significant correlation was found between ALFF and the ADHD RS-IV score in the ADHD group.

Low IQ is associated with ADHD[22, 23]. Given the non-random selection of groups, covarying for IQ would violate the univariate analysis of covariance (ANCOVA) assumptions and change the group effects in potentially problematic ways[24, 25]. However, to assess potential correlations between IQ and RS-fMRI measurements, we performed *post-hoc* analyses to examine the linear relationship between IQ and mean ReHo or ALFF for each ROI (nine ROIs for ReHo and one for ALFF) in each group. For the 20 pairs of correlations (10 ROIs for each group), only the ALFF-ROI in the ADHD group reached significance (r = −0.50, P = 0.03).

ReHo was shown to be more sensitive than ALFF to regional abnormality. However, the ReHo algorithm has an inherent spatial smoothing effect, and hence, the final

Table 1. Demographic characteristics

Variables	ADHD (n = 19)	Controls (n = 23)	t	P
Age (years)	13.3 ± 1.4	13.2 ± 1.0	0.22	0.83
Full-scale IQ	102.7 ± 10.4	113.5 ± 12.8	−2.98	0.005
ADHD RS-IV (parents)*				
Inattention score	18.72 ± 4.39	6.85 ± 4.98	7.76	<0.001
Hyperactivity/impulsivity score	13.56 ± 6.63	3.40 ± 2.26	6.19	<0.001
Total score	32.28 ± 9.42	10.25 ± 6.57	8.43	<0.001

ADHD RS-IV, ADHD Rating Scale-IV; *ADHD group: n = 18, 1 missing; Control group: n = 20, 3 missing.

Table 2. Regions exhibiting significant differences in ReHo or ALFF (FWHM = 6 mm) between the ADHD and control groups

Areas	BA	L/R	Volume (mm^3)	MNI (peak) x	y	z	*t*-value
Lower ReHo in ADHD group							
Cerebellum		R	3078	18	−84	−33	−4.67
Middle frontal gyrus	45	R	1296	48	45	12	−4.64
Cerebellum		L	1161	−33	−60	−30	−4.31
Cerebellum		R	3753	30	−75	−24	−4.19
Precuneus	5	R	1188	6	−48	75	−3.69
vMPFC[a]	32	R	1728	3	51	12	−3.46
	32	L		−3	54	3	−3.20
Higher ReHo in ADHD group							
Lingual gyrus/fusiform gyrus	18	R	1161	18	−78	−3	3.69
dACC[b]	32	R	1080	15	42	21	3.08
Lingual gyrus[b]	19	L	2106	−24	−60	−6	3.40
Higher ALFF in ADHD group							
Lingual gyrus/fusiform gyrus	18	R	3969	18	−81	−3	4.52

[a]Areas in right and left vMPFC merged into one cluster; [b]extended into the nearby white matters. BA, Brodmann area; dACC, dorsal anterior cingulate cortex; L/R, left/right; MNI, Montreal Neurological Institute coordinates; vMPFC, ventral medial prefrontal cortex.

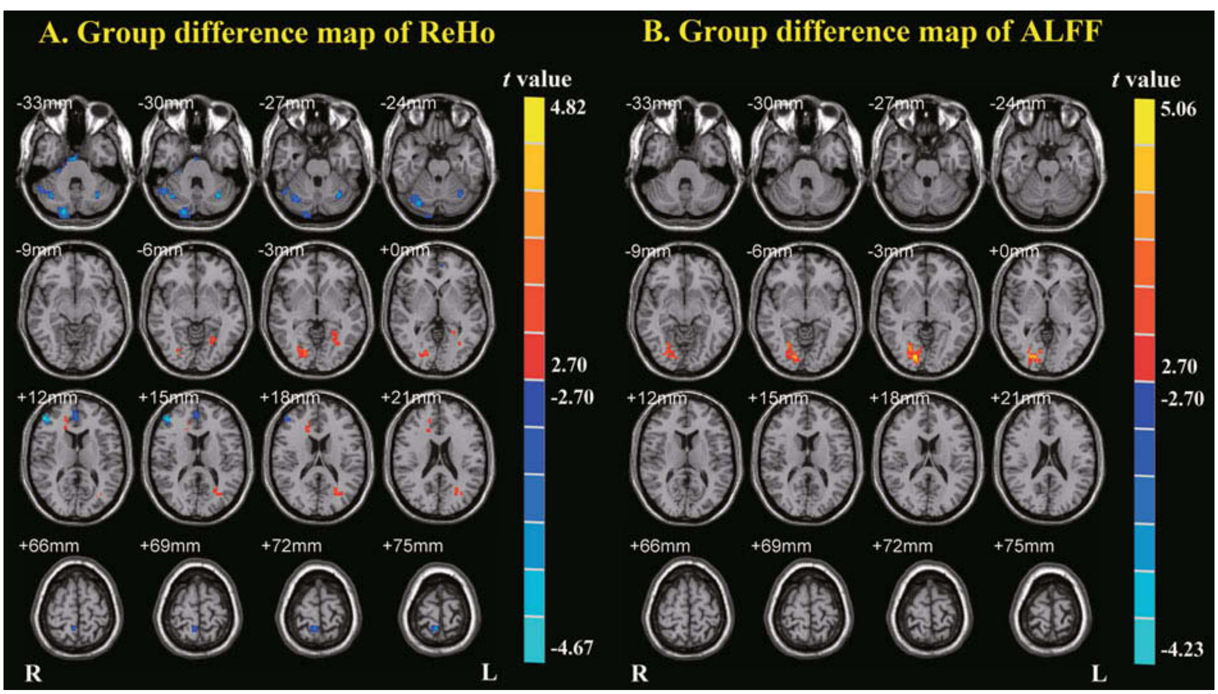

Fig. 1. Regions exhibiting differences in ReHo (A) and ALFF (B) between the ADHD and control groups. Cold colors indicate regions showing lower ReHo/ALFF in the ADHD group than the controls, and warm colors *vice versa*. Voxels with *P* <0.01 and cluster size >1080 mm^3 (corrected) were considered to show significant differences in ReHo and ALFF between the two groups. Full-width at half-maximum was 6 mm for both ReHo and ALFF. Left in the figures shows the right side of the brain.

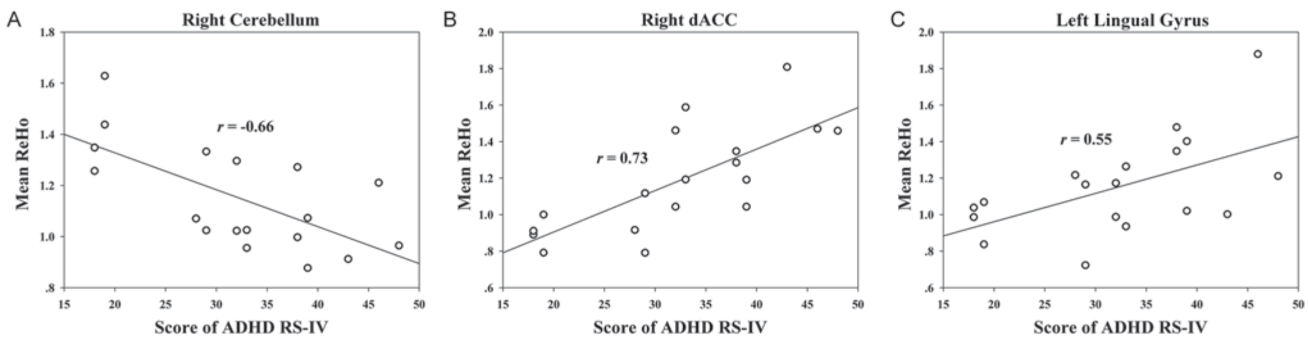

Fig. 2. Correlation between the severity of ADHD symptoms and ReHo in the right cerebellum (A), right dACC (B) and left lingual gyrus (C) in the ADHD group. A: The ReHo of the ROI in the right cerebellum (peak coordinates: 30, −75, −24) was negatively correlated with the ADHD RS-IV score (r = −0.66, P = 0.003). B: The ReHo of the ROI in the right dACC (peak coordinates: 15, 42, 21) showed a positive correlation with the ADHD RS-IV score (r = 0.73, P = 0.001). C: The ReHo of the ROI in the left lingual gyrus (peak coordinates: −24, −60, −6) showed a positive correlation with the ADHD RS-IV score (r = 0.55, P = 0.02). n = 18 (1 missing).

Table 3. Regions exhibiting significant differences in ALFF (FWHM = 12 mm) between the ADHD and control groups

Areas	BA	L/R	Volume (mm^3)	MNI (peak)			*t*-value
				x	y	z	
Lower ALFF in ADHD group							
Supramarginal gyrus	2/40	R	2376	69	−21	24	−4.05
Cerebellum		R	96	30	−72	−27	−3.89
Orbitofrontal cortex	38/47	L	459	−42	30	−18	−3.86
Middle temporal gyrus	21/38	L	540	−60	0	−24	−3.80
Middle frontal gyrus	6	R	378	42	0	63	−3.75
Supplementary motor area[a]	6	L	1161	−3	0	60	−3.49
	6	R		12	6	66	−3.12
Amygdala		R	270	18	6	−15	−3.37
Cerebellum		L	972	−6	−78	−21	−3.32
Rolandic operculum	48	R	486	66	0	9	−3.24
Middle frontal gyrus	8	R	378	33	21	54	−3.18
Posterior cingulate gyrus	30	L	270	0	−51	21	−2.91
Higher ALFF in ADHD group							
Lingual gyrus/fusiform gyrus	18/19	R	3267	21	−78	−3	4.08
Inferior frontal gyrus	47	L	405	−39	39	−3	3.63
Lingual gyrus/fusiform gyrus	18/19	L	2673	−21	−93	−12	3.27
Postcentral gyrus	4/3	L	918	−21	−30	72	3.53
Cuneus	18	L	1107	−9	−75	21	3.38
Middle frontal gyrus[b]	46	L	891	−27	39	21	3.20

[a]Areas in right and left supplementary motor area merged into one cluster; [b]extended into the nearby white matters; BA, Brodmann area; L/R, left/right; MNI, Montreal Neurological Institute coordinates.

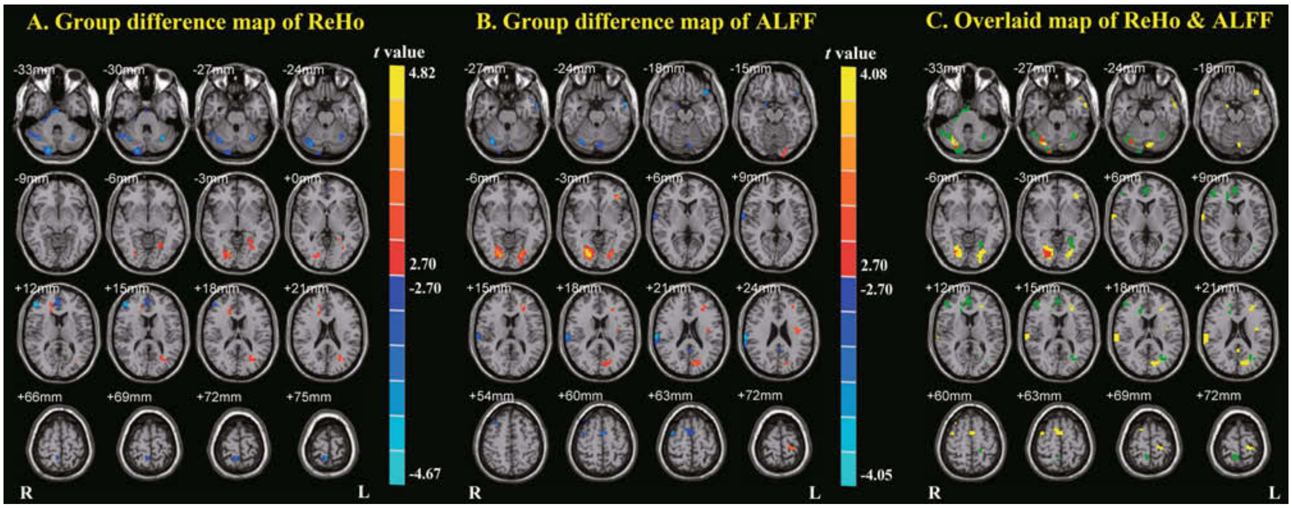

Fig. 3. Regions exhibiting differences in ReHo (A, FWHM 6 mm) and ALFF (B, FWHM 12 mm) between the ADHD and the control groups. Cold colors indicate regions showing lower ReHo or ALFF in the ADHD group than the control, while warm colors *vice versa*. Threshold for ReHo: *P* <0.01 and cluster size >1080 mm^3 (corrected); for ALFF: *P* <0.01 and cluster size >270 mm^3 (uncorrected). C: The overlaid map of A (green) and B (yellow). The overlapped regions are marked in red. Left in the figures shows the right side of the brain.

smoothing effect for ReHo would be larger than that for ALFF. This might bias the comparison between them. We therefore further re-conducted spatial smoothing with a larger FWHM of 12 mm for the ALFF map and a more lenient threshold (*P* <0.01 and cluster size >270 mm^3, uncorrected) was used. The two-sample *t*-test showed that, relative to controls, ADHD boys exhibited decreased ALFF in the right supramarginal gyrus, bilateral cerebellum, left orbitofrontal cortex (OFC), right dorsal lateral prefrontal cortex (DLPFC), bilateral supplementary motor area (SMA), right amygdala and left posterior cingulate cortex (PCC), and increased ALFF in the bilateral lingual and fusiform gyri, left ventral lateral prefrontal cortex (VLPFC), and left cuneus (Table 3, Fig. 3B). No significant correlation was found between the ALFF of any of the 17 new ALFF-ROIs and the ADHD RS-IV score in the ADHD group. The overlaid group difference map of ReHo (FWHM = 6 mm) and ALFF (FWHM = 12 mm) is shown in Fig. 3C. While more overlapped brain regions (right cerebellum and right lingual gyrus) were found by ReHo and ALFF, a few new regions with group differences (e.g. the right DLPFC, right supramarginal gyrus, bilateral SMA and left PCC) were found by ALFF alone.

DISCUSSTION

Using the ReHo method, we found widespread abnormalities of spontaneous brain activity in the fronto-cingulo-occipito-cerebellar areas; while using ALFF analysis, only one cluster in the right occipital cortex was identified using the same threshold and smoothing kernel as ReHo analysis. In addition, the only region detected by ALFF was almost completely included in the group difference map generated by the ReHo approach (only 3 mm between the peak voxels of the two clusters). However, when a larger smoothing kernel and a more lenient threshold were used for ALFF calculation, more overlapped abnormal regions (right cerebellum and right lingual gyrus) were revealed between the two methods. In addition, a few abnormal regions were found by ALFF alone, e.g. DLPFC, supramarginal gyrus, SMA and PCC (Fig. 3). This implies that ALFF may be complimentary to ReHo in depicting regional spontaneous neural activity in ADHD children, although false-positives cannot be ruled out for the uncorrected results. The current findings showed a similar pattern of between-group ReHo differences to that of Cao *et al.*[13] and ALFF differences to that of Zang *et al.*[6], since the samples in the three studies partly overlapped. Besides, compared with the previous ReHo and ALFF studies, we excluded participants with a history of medication administration to reduce confounding factors. This might account for the discrepancies between the current results and those of the previous two studies.

ALFF measures the amplitude of fluctuation of the spontaneous neural activity at the single-voxel level, while ReHo reflects the local synchronization of spontaneous neural activity between neighboring voxels. It seems that the neurophysiology of ALFF is more straightforward than that of ReHo. LFFs are associated with activity of the gamma band in monkeys[26], the delta band in rats[27], and the alpha band in humans[28, 29]. High local synchronization was revealed between the local field potentials from multiple cortical electrodes with a physical distance ranging from 2.6 mm to 10.6 mm in an electrophysiological study, and such local synchronization could be modulated by stimulation[30]. The physical distance between electrodes is similar to that of neighboring voxels in ReHo. The local synchronization of local field potentials may help understand the neurophysiological mechanism of ReHo.

Although ReHo and ALFF have been used in tens of studies focused on different brain disorders, no previous report has compared their sensitivity in the same dataset. Here, we found that: (1) ReHo may be more sensitive than ALFF to regional abnormalities, at least in boys with ADHD; and (2) ALFF may be complementary to ReHo in measuring local spontaneous activity, although false-positives cannot be ruled out for the uncorrected results. A possible explanation of the higher sensitivity of ReHo than ALFF is that the ReHo algorithm takes the dynamic features of the time-courses of 27 neighboring voxels into account, but ALFF calculates the overall fluctuations of the time-course of a single voxel. The current results suggest that abnormal local synchronization may be a sensitive index for ADHD. A recent study[31] showed that the effect of methylphenidate hydrochloride (MPH) on inter-regional synchronization (fronto-striatal and fronto-cerebellar connections) is more evident than its modulation of regional activation strength in boys with ADHD during sustained attention, pointing to a predominant synchronization dysfunction of the network in ADHD. Neuronal synchrony facilitates the coordination and organization of information processing in the human brain across several spatial and temporal ranges[32], which is considered to be the mechanism underlying inter-regional functional connectivity[33]. By measuring the synchrony of intra-regional fluctuations, we believe ReHo reflects the coordination of regional neuronal activity subserving similar goals or representations. Here, we found significant correlations between symptom scores and ReHo but not ALFF, which also suggested that ReHo may be more sensitive than ALFF to local abnormalities in ADHD. However, with a larger smoothing kernel and a more lenient threshold, ALFF detected a few abnormal regions that were not detected by ReHo. Although we could not exclude false-positives, ALFF seems to be complementary to ReHo analysis for investigations of local abnormalities. Thus, future studies should be carried out on more datasets, and a gold-standard dataset with optimized computational parameters will help further evaluate the sensitivity and specificity of these methods.

Using both ReHo and ALFF analyses, hyperactivity of the visual cortex in children with ADHD was identified in the current study, which is consistent with many previous resting-state findings[6, 13, 34, 35]. Effective treatment with MPH significantly reduces regional cerebral blood flow (rCBF) in the visual cortex of ADHD children[35-37]. Increased activity in the visual cortex of ADHD patients is considered to be associated with the inability to suppress responsiveness to irrelevant visual stimuli from the environment, which may result in inattention problems[35]. The close relationship between ADHD symptoms and activity in the left lingual gyrus found in our study may serve as supportive evidence.

In our study, the fronto-cingulo-parieto-cerebellar circuits, including the VLPFC, dACC, superior parietal cortex and cerebellar areas, showed mainly decreased local synchronization in ADHD during the resting state. These circuits are known as the cognitive-attentional network, underlying important higher brain functions such as executive control, cognition, selective and divided attention, vigilance and working memory[38, 39]. Resting-state[40] and cognitive[41, 42] neuroimaging findings have consistently shown hypoactivity in these circuits in ADHD patients. And activity in the cerebellum is correlated with the severity of ADHD symptoms[43] or the effect of MPH treatment[36], which are in line with our correlation results. MPFC, the anterior hub of the default network, exhibits reduced connectivity with the posterior hub (PCC) in

ADHD adults[44, 45] and in children with ADHD[46]. Besides, abnormalities in the inter-regional synchronization between the cognitive-attentional network and default network have been reported in ADHD patients[14, 44]. Thus we hypothesized that the mainly decreased local activity found in the current study in regions of the cognitive-attentional network and the default network of ADHD children may be associated with altered functional synchronization between them, which may underlie the attention lapses in ADHD[47].

In our study, IQ was lower in ADHD. Lower IQ is associated with ADHD in the general population[22, 23]. When the covariate is intrinsic to the condition, and hence differs between groups, it is inappropriate to “adjust” group effects for differences in the covariate because the group effect would be altered in potentially problematic ways, leading to spurious results[24, 25]. Anyway, to explore the potential confounding effect, we performed correlation analysis between IQ and RS-fMRI measures in each group for the 10 ROIs showing significant between-group differences. No significant correlations were found, except for the ALFF-ROI in the ADHD group. These results suggested that the IQ difference was unlikely to account for the group difference of RS-fMRI measurements.

In conclusion, our study showed for the first time that ReHo may be more sensitive than ALFF to regional abnormalities, at least in boys with ADHD. And the results imply that ALFF may be complementary to ReHo for measuring local spontaneous activity. Therefore, combination of the two methods could reveal a more comprehensive pathophysiological framework for ADHD. More datasets and, especially, a gold standard dataset will be helpful to evaluate the sensitivity and specificity of these methods. Further, the current study focused only on comparison between two local measures. Actually, analytic methods for functional connectivity, including seed-based linear correlation analysis and independent component analysis, are more widely used than local measures in RS-fMRI studies. So comparisons between functional connectivity methods are needed in future studies.

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