Sci. Bull. (2016) 61(9):682–692
DOI 10.1007/s11434-015-0823-y

www.scibull.com
www.springer.com/scp

Article

Life & Medical Sciences

Frequency-specific abnormalities in regional homogeneity among children with attention deficit hyperactivity disorder: a resting-state fMRI study

Xiaoyan Yu · Binke Yuan · Qingjiu Cao · Li An · Peng Wang · Alasdair Vance · Timothy J. Silk · Yufeng Zang · Yufeng Wang · Li Sun

Received: 22 March 2015 / Revised: 5 May 2015 / Accepted: 11 May 2015 / Published online: 17 June 2015

Abstract Although many functional magnetic resonance imaging (fMRI) studies have investigated the neurophysiology of attention deficit hyperactivity disorder (ADHD), the existing studies have not yielded consistent findings. This may be related to the different properties of different frequency bands. To investigate the frequency-specific regional homogeneity (ReHo) of spontaneous neural activities in ADHD, the current study used resting-state fMRI to explore the ReHo properties of five frequency bands, slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), slow-2 (0.198–0.25 Hz) and the extra-low frequency (0–0.01 Hz), in 30 drug-naive boys with ADHD and 30 healthy controls. Compared with controls, the ADHD group showed decreased ReHo in the default mode network (DMN) including the medial prefrontal cortex and precuneus, middle frontal gyrus and angular gyrus. ADHD patients also showed increased ReHo in the posterior cerebellum. Significant interactions between frequency band and group were observed predominantly in the dorsolateral prefrontal and parietal cortices, orbital frontal cortex, supplementary motor area, inferior occipital gyrus, thalamus and anterior cerebellum. In particular, we found that the between-group difference in the extra-low frequency band (0–0.01 Hz) seemed to be greater than that in the other frequency bands for most brain regions. The findings suggest that ADHD children display widespread abnormalities in regional brain activity, particularly in the DMN and attention network, and these abnormalities show frequency specificity.

Keywords Attention deficit hyperactivity disorder (ADHD) · Resting state · Regional homogeneity (ReHo) · Frequency-specific

SPECIAL TOPIC Human Functional Connectomics: Focus on Brain Development

Electronic supplementary material The online version of this article (doi:10.1007/s11434-015-0823-y) contains supplementary material, which is available to authorized users.

X. Yu · Q. Cao · L. An · P. Wang · Y. Wang · L. Sun (✉)
Peking University Sixth Hospital/Institute of Mental Health, Beijing 100191, China
e-mail: sunlioh@bjmu.edu.cn

X. Yu · Q. Cao · L. An · P. Wang · Y. Wang · L. Sun
Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing 100191, China

B. Yuan · Y. Zang
Center for Cognition and Brain Disorders, Hangzhou Normal University, Hangzhou 311121, China

B. Yuan · Y. Zang
Zhejiang Key Laboratory for Research in Assessment of Cognitive Impairments, Hangzhou 311121, China

A. Vance
Academic Child Psychiatry Unit, Department of Pediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, VIC 3052, Australia

T. J. Silk
Developmental Imaging, Murdoch Childrens Research Institute, Department of Pediatrics, University of Melbourne, Melbourne, VIC 3052, Australia

1 Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood onset disorders and is characterized by developmentally inappropriate inattentiveness, impulsivity and hyperactivity. The worldwide prevalence of this disorder is estimated to be 8 %–12 % [1]. Although the etiology of ADHD remains unclear, neuroimaging studies have observed dysfunction in brain regions such as the prefrontal and parietal cortices, cingulate cortex, caudate, basal ganglia and cerebellum [2–7].

Resting-state fMRI (RS-fMRI) has been widely applied to explore the functional abnormalities of ADHD. Many RS-fMRI studies have reported abnormal functional connectivity (FC) of certain brain regions and networks in patients with ADHD. For example, researchers have found abnormal connectivity between the dorsal anterior cingulate cortex (dACC) and the posterior cingulate cortex (PCC)/precuneus (PCu), suggesting abnormal activation in the default mode network (DMN) of children [8, 9] and adults [10] with ADHD. In addition to these FC abnormalities, abnormal local activities have been identified. Regional homogeneity (ReHo), a widely used approach to measure the similarity of the time series of a given voxel with its neighbors within a single region, provides important information regarding the local temporal synchrony of the brain regions [11]. ReHo has been used to explore regional spontaneous low-frequency oscillation activities in patients with schizophrenia [12], major depression [13], Parkinson's disease [14], epilepsy [15] and ADHD [16, 17]. Cao et al. [17] found decreased ReHo in the frontal–striatal–cerebellar circuits but increased ReHo in the occipital cortex of ADHD children. Cheng et al. [18] observed decreased ReHo in the PCu and medial frontal gyrus but increased ReHo in the cerebellum, cuneus, thalamus, precentral gyrus and cingulate gyrus in ADHD patients.

Despite recent advances, most previous RS-fMRI studies focused on low-frequency oscillations (0.01–0.1 Hz). Brain oscillation data obtained from electroencephalography (EEG) cover a wide range of frequencies, which can then be divided into multiple oscillatory bands. These oscillatory bands have been found to be related to different mechanisms and associated with different brain states [19]. Previous reviews noted that an understanding of the physiological mechanisms of self-emerging oscillations would not only provide insight into their functions but also assist in the diagnosis and treatment of brain disorders [19, 20]. The above 0.1-Hz fMRI signal is thought to be related to cardiac or respiratory factors [21] and is always removed from data analysis. However, recent studies found more to the story. Such signals also reflect spontaneous neural activity. Malinen et al. [22] suggested that fluctuations from 0.12 to 0.25 Hz might be related to altered activity of the autonomic nervous system in patients with chronic pain. Recently, Zuo et al. [23] subdivided the entire frequency range into four bands: slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz). They found different contributions of the slow-5 and slow-4 bands to low-frequency oscillation amplitudes in specific regions such as the basal ganglia, thalamus and PCu in healthy participants [23, 24]. Employing ReHo, Yu et al. [25] investigated the frequency characteristics of neural activity in patients with schizophrenia and found different ReHo abnormalities between the slow-5 and slow-4 frequencies in brain regions, including the inferior occipital gyrus (IOG) and caudate. Other studies have shown significant interactions between different frequency bands among patients with mild cognitive impairment and schizophrenia [26, 27]. A recent study used amplitude of low-frequency fluctuation (ALFF) to investigate the characteristics of five frequency bands in patients with late-onset depression. They found that patients with late-onset depression showed frequency-specific ALFF abnormalities in widespread brain regions, which may be related to cognitive dysfunction [28]. All of these studies have provided evidence that brain activity is sensitive to specific frequency bands. To our knowledge, however, no studies have examined the properties of different frequency bands in children with ADHD.

Thus, in the current study, we explored the ReHo differences between ADHD children and healthy controls across five frequency bands (for details, see Sect. 2). We expected ReHo abnormalities in children with ADHD to show frequency specificity.

2 Materials and methods

2.1 Participants

The participants included 30 stimulant-naïve boys who were diagnosed with ADHD and 30 age-matched healthy male controls (aged 8–14 years). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Detailed demographic information and the clinical characteristics of the participants are listed in Table 1. Participants who met the criteria of left-handedness; lifetime history of head trauma with loss of consciousness; history of neurological illness or psychiatric disorders, including schizophrenia, affective disorders, anxiety, Tourette's disorder, pervasive developmental disorder and mental retardation; or a full-scale intelligence

Table 1 Participant demographic and clinical information

Variables	Control group ($n = 30$)	ADHD group ($n = 30$)	t value	P value
Age (years)	10.3 ± 1.7	10.2 ± 1.7	0.376	0.708
Full-scale IQ score	121.1 ± 13.9	106.2 ± 14.5	4.058	<0.001
ADHD RS-IV				
Inattention	17.0 ± 3.8	27.6 ± 4.3	−9.826	<0.001
Hyperactivity/impulsivity	15.6 ± 3.8	21.2 ± 5.4	−4.516	<0.001
Total scores	32.6 ± 6.6	48.8 ± 6.9	9.090	<0.001
Mean head motion	0.41 ± 0.19	0.42 ± 0.20	0.217	0.829

quotient (IQ) score < 80 were excluded from our study [29]. Patients with comorbid conduct disorder (CD) or oppositional defiant disorder (ODD) were not excluded. All patients with ADHD were outpatients of the Institute of Mental Health, Peking University. The ADHD diagnosis was made using a semi-structured diagnostic interview, the Clinical Diagnostic Interviewing Scale (CDIS) [30], based on DSM-IV criteria. Fifteen of the 30 boys with ADHD met the criteria for the combined type, 14 met the criteria for the predominantly inattentive type, and 1 met the criteria for the predominantly hyperactivity/impulsivity type. Twelve patients also had comorbid ODD, and 1 had comorbid CD.

The healthy controls were recruited from a local primary school. They were also assessed using CDIS but did not conform to an ADHD diagnosis, and their exclusion criteria were the same as those for the ADHD group.

The study was approved by the Research Ethics Review Board of the Institute of Mental Health, Peking University. Written informed consent was obtained from the parents of the participants, and all of the children agreed to participate.

2.2 MRI data acquisition

The MRI data were acquired using a Siemens Trio 3T scanner at the Imaging Center for Brain Research, Beijing Normal University. The participants lay supine, and a head strap and foam pads were used to minimize their head movement. The participants were verbally asked to remain still and to relax with their eyes closed while attempting not to think of anything in particular during the RS-fMRI scanning. The images were collected using an echo planar imaging (EPI) sequence: 33 axial slices, repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 90°, thickness/skip = 3.5/0.7 mm, field of view (FOV) = 200 × 200 mm^2, acquisition matrix = 64 × 64, 240 volumes. Individual 3D T1-weighted images were acquired with the following parameters: 128 sagittal slices, TR = 2,530 ms, TE = 3.39 ms, slice thickness/gap = 1.33/0 mm, flip angle = 7°, inversion time (TI) = 1,100 ms, in-plane resolution = 256 × 192 and FOV = 256 × 256 mm^2.

2.3 Data processing

The data analysis was performed using the Data Processing Assist for RS-fMRI (DPARSF) [31], which integrates Statistical Parameter Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm) and the RS-fMRI Data Analysis Toolkit (REST) (http://www.restfmri.net) [32]. The data processing included the following steps: (1) The first 10 volumes were discarded due to scanner calibration and participant adaptation to the fMRI scanning. (2) Slice timing and (3) head motion correction were performed. No participants were excluded from the study due to excessive motion (defined as more than 3 mm of translation or more than 3 degrees of rotation in any direction). (4) Individual 3D structural images were first co-registered to the mean functional realigned image and then segmented into gray matter, white matter (WM) and cerebrospinal flow (CSF). (5) The functional images were spatially normalized to the Montreal Neurological Institute (MNI) space (resampled voxel size = 3 × 3 × 3 mm^3) using the transformation matrix that was obtained in step (4). (6) The temporal linear trend was removed from the normalized functional data. (7) To reduce the influence of motion and physiological noise with regard to the RS-fMRI signal, a regression was conducted with the signals of WM, CSF, global signal (GS) and the Friston 24-parameter head motion as covariates. (8) Temporal band-pass filtering was performed. The data were filtered in slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 bands (0.198–0.25 Hz; see [24]). In addition, the extra-low frequency band (0–0.01 Hz) was examined given that a recent study suggested that this frequency band is physiologically meaningful [33].

Then, individual ReHo maps were generated by calculating the Kendall's coefficient of concordance (KCC) of the time series of the 27 nearest neighboring voxels in a voxel-wise manner [11]. For standardization purposes, the individual ReHo maps were divided by their own global mean values within a whole-brain mask. Finally, spatial smoothing was conducted on each ReHo map with a Gaussian kernel of 6 × 6 × 6 mm^3 full width at half maximum.

2.4 Statistical analyses

Between-group statistical comparisons of the demographic and clinical data were performed using SPSS 19.0 (http://www.spss.com). The mean head motion parameters [34] were also compared between groups using a two-sample t test to control for the effect of participants' head motion. To identify the frequency-specific differences in ReHo values between the ADHD and control groups, a whole-brain voxel-wise mixed-model ANOVA was performed using 3dANOVA in AFNI (http://afni.nimh.nih.gov/afni/) [35], with frequency band entered as the repeated factor (type = 5). To correct for multiple comparisons in this voxel-wise assessment, a threshold of $P < 0.01$ (main effect of group: $F(1, 58) > 7.103$; interaction effect: $F(4, 232) > 3.404$) and cluster sizes $\geq$1080 mm^3 (40 voxels), which corresponded to a corrected $P < 0.05$ using AlphaSim, were set [36]. Lastly, post hoc two-sample t tests were performed on the peak voxels in regions that were identified in the main effect of group (SPSS 19.0).

3 Results

3.1 Demographic information

No significant between-group differences were found with regard to participants' age (control: 10.2 ± 1.7; ADHD: 10.3 ± 1.7, $P = 0.708$) or mean head motion (control: 0.41 ± 0.19; ADHD: 0.42 ± 0.20, $P = 0.829$). Compared with the controls, the patients with ADHD had lower full-scale IQ scores (control: 121.1 ± 13.9; ADHD: 106.2 ± 14.5, $P < 0.001$), higher inattention scores (control: 17.0 ± 3.8; ADHD: 27.6 ± 4.3, $P < 0.001$), and higher hyperactivity/impulsivity scores (control: 15.6 ± 3.8; ADHD: 21.2 ± 5.4, $P < 0.001$) and higher ADHD RS-IV total scores (control: 32.6 ± 6.6; ADHD: 48.8 ± 6.9, $P < 0.001$; Table 1).

3.2 The main effect of group on ReHo

The two-way repeated measures ANOVA found a significant main effect of group ($P < 0.05$, corrected), as shown in Table 2 and Fig. 1. Further post hoc two-sample t tests showed that ADHD patients had significantly decreased ReHo in the left medial prefrontal cortex (MPFC), middle frontal gyrus (MFG), right angular gyrus and bilateral PCu. Furthermore, ADHD patients showed increased ReHo in the right posterior cerebellum.

With regard to the left MPFC, right angular gyrus and bilateral PCu, upon visual inspection, the low frequency bands (extra-low frequency, slow-5 and slow-4) contributed more to the between-group difference than did the high frequency bands. With regard to the left MFG and right posterior cerebellum, the extra-low frequency, slow-3 and slow-2 bands contributed more to the differences in ReHo than did the slow-5 and slow-4 bands (Fig. 2).

3.3 The interaction effect between frequency band and group

Significant interaction effects were found between frequency band and group ($P < 0.05$, corrected) in the following brain regions: the bilateral inferior/medial orbital frontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) including the MFG and superior frontal gyrus (SFG), supplementary motor area (SMA) extending to the middle cingulate cortex (MCC) and left postcentral gyrus (PoCG), parietal cortices including the superior and inferior parietal gyrus (SPG and IPG), supramarginal gyrus, left IOG including the calcarine and lingual gyrus, right fusiform, left thalamus and right anterior cerebellum (Table 3; Fig. 3).

For example, ADHD patients showed decreased ReHo values in the low frequency bands (e.g., the extra-low frequency and slow-5 bands) but increased values in the high frequency bands (e.g., slow-3 and slow-2 bands) with regard to the bilateral inferior/middle OFC and right anterior cerebellum compared with the controls. ADHD patients showed increased ReHo values in the low frequency bands (e.g., the extra-low frequency band) but decreased values in the high frequency bands (e.g., slow-2) with regard to the left calcarine and right fusiform. The differences were large in the low frequency bands but gradually reduced as the frequency increased in the left

Table 2 Brain regions showing significant differences between the control and ADHD groups on ReHo

Brain regions	BA	R/L	x	y	z	Cluster size	Peak F value
ADHD group < control group							
MPFC	9/10	L	−3	63	30	1,350	19.31
Angular gyrus	39/40	R	51	−51	33	1,161	14.53
PCu		R/L	−6	−48	39	2,133	16.39
MFG	44/45	L	−42	27	36	1,971	13.68
ADHD group > control group							
Cerebellum		R	24	−48	−57	1,350	12.37

MPFC medial prefrontal cortex, *PCu* precuneus, *MFG* middle frontal gyrus, *BA* Brodmann's area

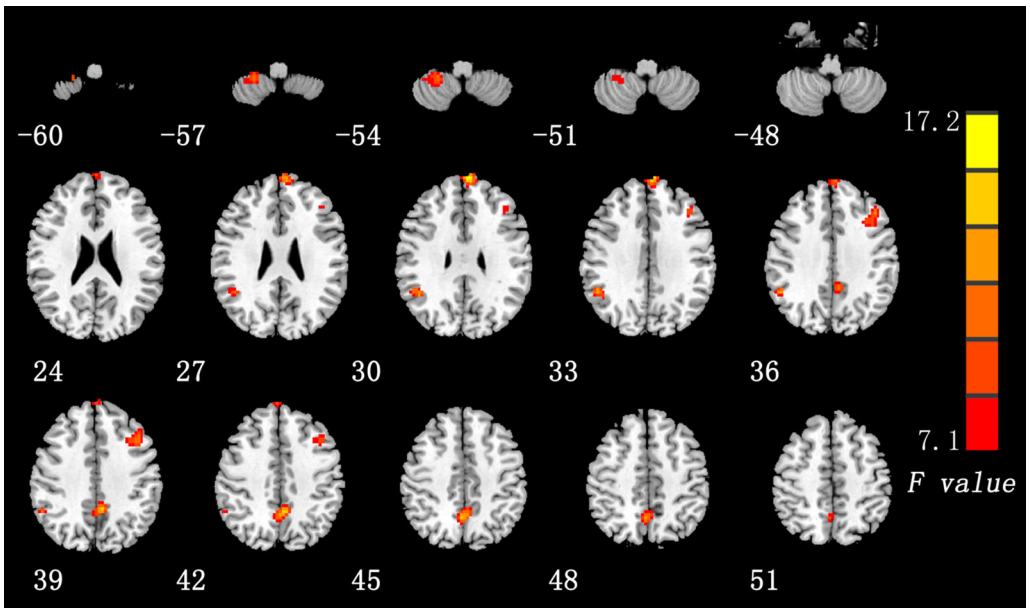

Fig. 1 Main effect of group on ReHo. The results were obtained by combining the 3dANOVA in AFNI ($P < 0.05$, ≥40 voxels, corrected). R: right; L: left

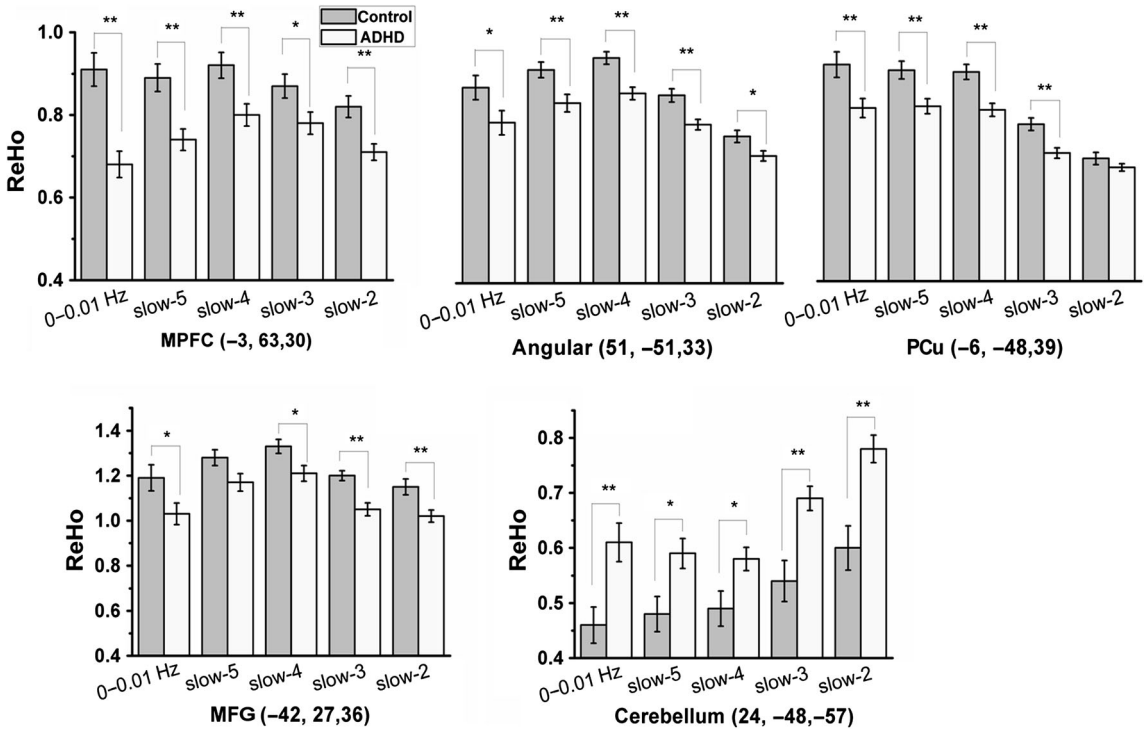

Fig. 2 Regions of ReHo showing a significant main effect of group across different frequency bands. The ReHo values of the peak coordinates of these brain regions were extracted and are shown here. The frequency bands were defined as follows: extra-low frequency (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz). ReHo: regional homogeneity; $^{*}P < 0.05$; $^{**}P < 0.01$, uncorrected

thalamus, right supramarginal gyrus and bilateral MFG (Fig. 4).

Interestingly, we found that the difference in the extra-low frequency band (0–0.01 Hz) was greater than that in the other four frequency bands for most brain regions, typically including the right SFG and bilateral SMA (Fig. 4).

We also found a significant main effect of frequency band, which nearly covered the whole brain region.

Table 3 Brain regions showing a significant interaction between frequency band and group on ReHo

Brain regions	BA	R/L	*x*	*y*	*z*	Cluster size	Peak *F* value
Cerebellum		R	45	−54	−36	1,215	6.90
IOG/calcarine	18	L	−15	−99	−9	1,944	5.64
OIFC/OMFC	11/47	R	33	45	−15	3,159	7.76
OIFC/OMFC	11/47	L	−33	48	−15	1,647	9.81
Fusiform	37	R	42	−42	−9	297	5.82
Thalamus		L	−6	−12	9	1,107	7.68
Supramarginal	40	R	39	−42	36	3,348	9.65
SFG	8/9	R	18	33	51	1,323	10.11
MFG/SFG	6/8	L	−24	6	54	2,187	8.86
PoCG	3/4/43	L	−60	−12	42	1,809	7.67
SMA		R/L	−6	−3	48	1,377	6.45
SPG/IPG	7	L	−30	−3	48	972	5.71

IOG inferior occipital gyrus, *OIFC/OMFC* inferior/medial orbital frontal cortex, *SFG/MFG* superior/middle frontal gyrus, *SMA* supplementary motor area, *PoCG* postcentral gyrus, *SPG/IPG* superior/inferior parietal gyrus, *BA* Brodmann's area

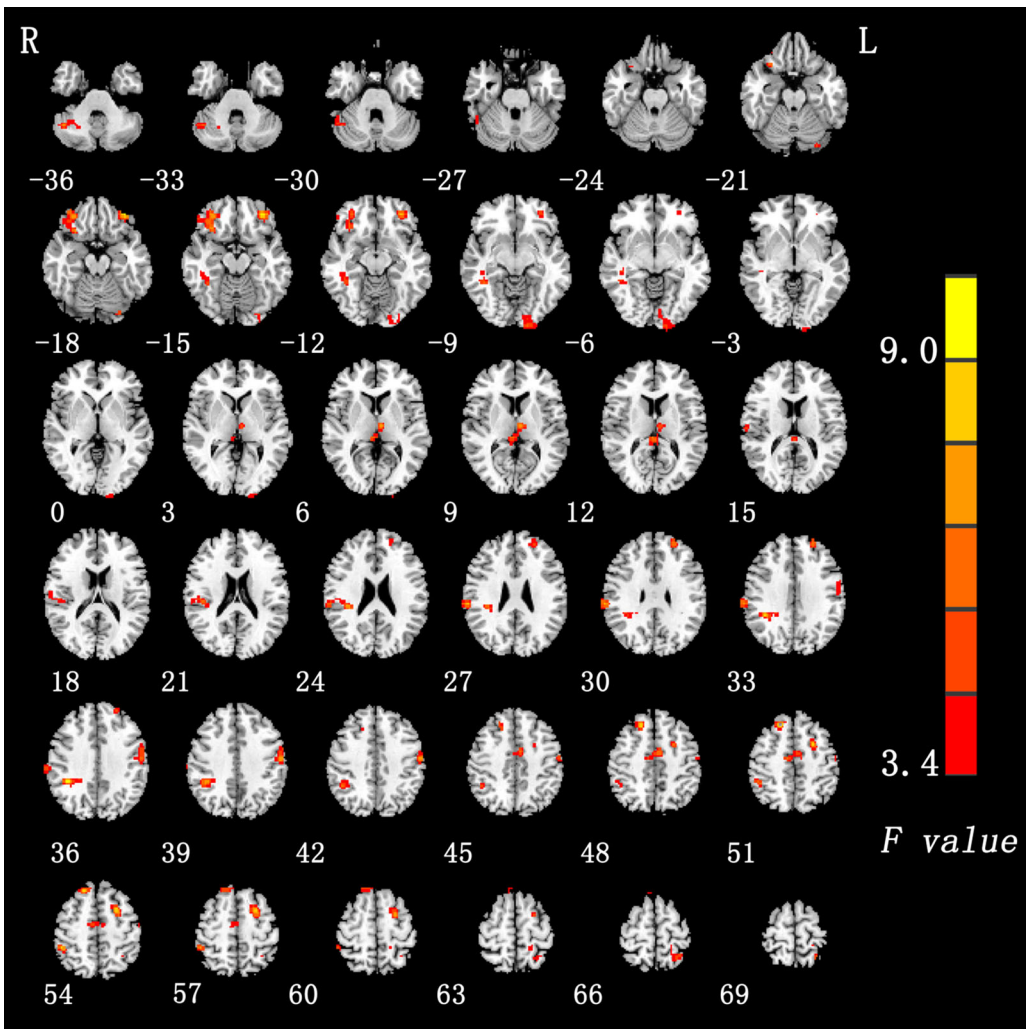

Fig. 3 Interaction between frequency band and group on ReHo. The results were obtained using 3dANOVA in AFNI ($P < 0.05$, ≥40 voxels, corrected). R: right; L: left

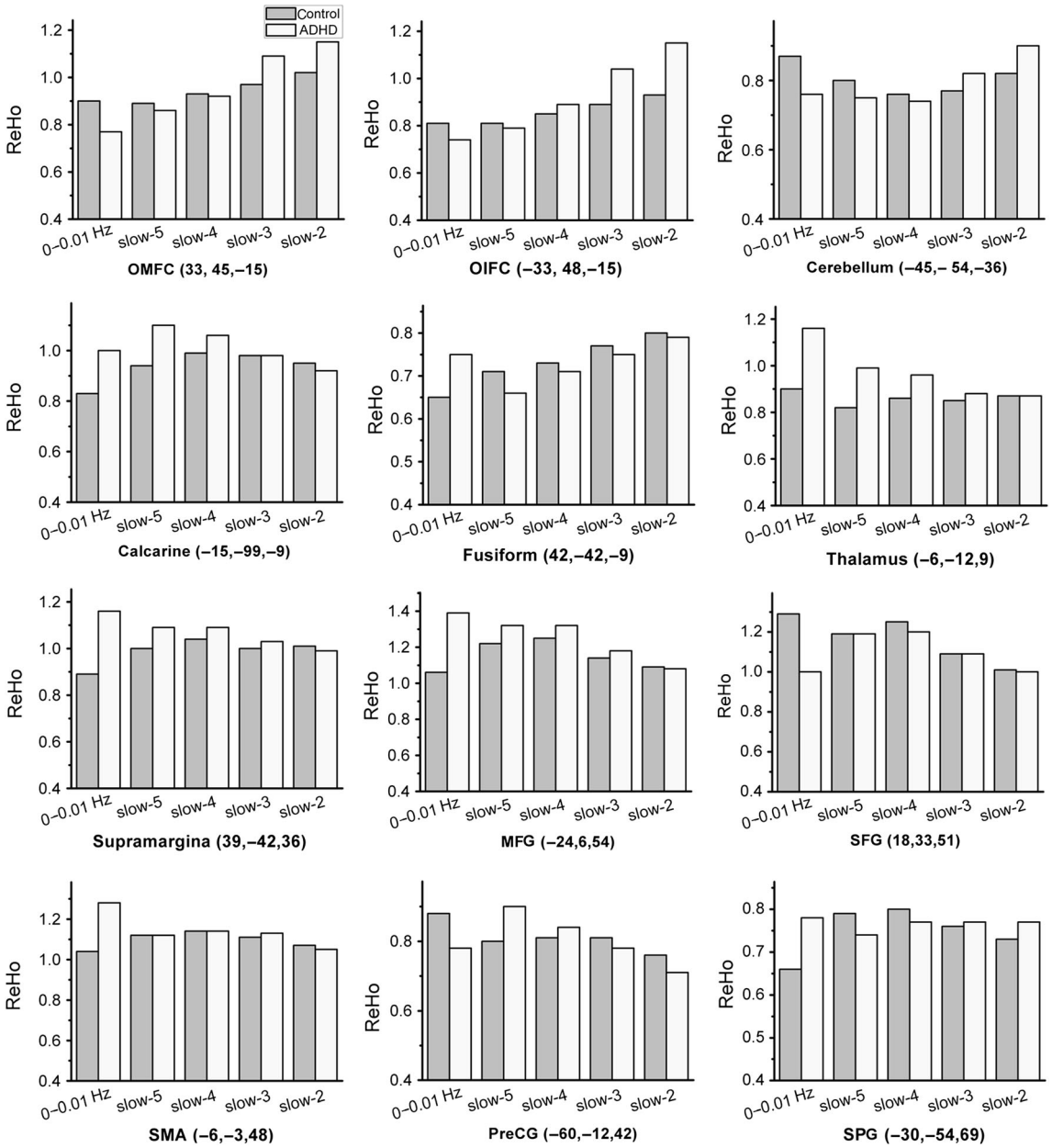

Fig. 4 Regions of ReHo showing an interaction effect in different frequency bands. The ReHo values of the peak coordinates of these brain regions were extracted and are shown here. The frequency bands were defined as follows: extra-low frequency (0–0.01 Hz), slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz) and slow-2 (0.198–0.25 Hz). ReHo: regional homogeneity

However, this main effect is beyond the scope of the current study and thus is not shown here (Fig. S1).

3.4 The effects of the regression with nuisance covariates

In addition, to explore the effect of the covariate signals (including WM, CSF, GS and head motion) on the results, we re-conducted fMRI data processing in a regression without nuisance covariates. The results somewhat differed from those found when including these signals as covariates. Specifically, only the left middle temporal gyrus (MTG) showed a significant main effect of group (Table S1 and Fig. S2), while significant interactions between frequency band and group were primarily found in the left cerebellum, left fusiform, right olfactory/caudate, bilateral temporal gyrus frontal lobe including bilateral inferior OFC and right SFG, left PoCG, SPG and PCu/PCC, and bilateral paracentral lobule (Table S2, Fig. S4).

Furthermore, as there is controversy concerning the effect of GS on RS-fMRI data, we also re-performed the data processing in a regression that included only the signals of WM, CSF and head motion (but not GS) as covariates to further explore the potential effect of GS on the data. We found roughly similar results as those found while regressing out GS. Specifically, we found significant main effects of group in the right cerebellum, right calcarine, left MPFC and MFG (Table S3 and Fig. S5) and interaction effects between frequency band and group primarily in the right cerebellum, bilateral OIFG/OMFG, right MPFC, bilateral SFG/MFG and SMA and left lingual gyrus (Table S4 and Fig. S6).

4 Discussion

This study investigated the ReHo properties of different frequency bands in children with ADHD. We found that ADHD children showed decreased ReHo patterns in brain regions, including the DMN including the MPFC and PCu, MFG and angular gyrus and increased ReHo in the posterior cerebellum. In addition, we found significant interactions between frequency band and group in attention network regions, including the DLPFC and parietal cortex, SMA, IOG, thalamus and anterior cerebellum. These results indicate that the ReHo abnormalities related to ADHD are associated with specific frequency bands. We also found that the between-group difference in the extra-low frequency band was greater than that in the other frequency bands for most of the abovementioned brain regions; moreover, the high frequency bands (slow-3 and slow-2) showed specificity in certain brain regions. The results suggest that children with ADHD show widespread abnormal ReHo in brain regions, including the DMN and attention network, and these abnormalities are specific to different frequency bands.

4.1 The main effect of group

One of the primary findings was that the ADHD group showed decreased ReHo in brain regions, including the MPFC, PCu, angular gyrus and MFG, and increased ReHo in the cerebellum. The low frequency bands (e.g., extra-low frequency, slow-5 and slow-4) contributed more to the between-group differences in the MPFC, PCu and angular gyrus than did the high frequency bands, while the extra-low frequency, slow-3 and slow-2 bands contributed more to the differences in the MFG and cerebellum than did the slow-5 and slow-4 bands. These findings indicate that the frequency sensitivity of the abnormalities is variable across different regions in ADHD children. The MPFC and PCu are "core hubs" of the DMN. The MPFC likely mediates the dynamic interplay between emotional processing and cognition functions within the DMN activity [37]. The decreased ReHo pattern in the MPFC is consistent with a previous resting-state magnetoencephalography (MEG) study that indicated a robust broadband decrease of neuronal activity in the MPFC in ADHD patients [38]. The PCu/PCC is associated with episodic memory [39] and shows reduced activity in ADHD patients [40]. Reduced FC between the anterior and posterior default mode components has been reported among adults with ADHD [10]. A similar resting-state study concerning cohesiveness within a specified functional network showed that ADHD patients displayed reduced network homogeneity within the DMN, particularly between the PCu and other DMN regions [41], which is consistent with the current results. Because the DMN is related to attentional control [42], working memory [10], executive behavior [43] and reward processing [44], the coincident findings might confirm these functional deficits in ADHD children.

The cerebellum, which has frequently displayed abnormalities in ADHD patients, is related to motor movements, attention, cognitive control and timing [45–48]. The enhanced cerebellum activation observed in ADHD patients might be a compensatory mechanism of the posterior portion of the attention network for sustained attention [46, 47]. Concerning the between-group differences related to the cerebellum and MFC, we found that the dysfunctions of these two regions were more sensitive in the high frequency and extra-low frequency bands compared with the slow-5 and slow-4 bands (i.e., the traditional windows for band-pass filtering). These frequency-specific ReHo properties of certain brain areas might arise from disparate cytoarchitectures or synaptic types [49]. If this is the case, these findings might partially aid in the understanding of the pathophysiological mechanisms of ADHD.

4.2 The interaction effect between frequency band and group

A significant interaction between frequency band and group was found in several regions, including the DLPFC and parietal cortex, SMA, IOG, and thalamus and anterior cerebellum. These regional abnormalities were frequently reported, and they contributed to the dysfunctions of the cognitive–attention network [3] in ADHD patients.

The DMN is negatively correlated with the task-positive network [50, 51]. This might reflect a binding mechanism between introspective and extrospective attentional orientations [52]. Reduced or disrupted anti-correlations reflect disparity and variability between the two networks, which could result in relationship deficits between introspective and extrospective attentional orientation in ADHD patients. The BOLD signal across different frequency bands is

thought to be related to the integration between individual neuronal processes [53]. These significant interaction effects typically indicate that complex abnormalities of spontaneous brain activity are associated with specific frequency bands in ADHD children. As mentioned above, several rhythms can temporally coexist in the same or different structures, and neighboring frequency bands within the same neuronal network are typically associated with different brain states and compete with each other [19]. For instance, in the bilateral OFC, ADHD children showed decreased ReHo values in the low frequency bands but increased ReHo values in the high frequency bands compared with controls. EEG studies have indicated that elevated relative theta power and reduced relative alpha and beta combined with elevated theta/alpha and theta/beta ratios are most reliably found in ADHD patients [54]. Recent evidence has suggested that the power of EEG oscillations significantly contributes to spontaneous local fluctuations in the resting-state BOLD signal in humans [55, 56]. Although the correlation between EEG and BOLD signals remains unclear, the current results may provide partial support for such a correlation. Additional work combining EEG and RS-fMRI synchronous recordings would be helpful in understanding their relationship.

According to our results, some brain regions such as the PCu showed greater decreases in widespread low frequency bands (e.g., from the extra-low frequency to slow-3) than in higher frequency bands (slow-2), while other brain regions such as the OFC displayed greater abnormality in high frequency bands (e.g., slow-3 and slow-2). The frequency bands that contribute more to this abnormality could indicate the neurophysiological mechanisms of brain regions. This notion is similar to that found in a previous study that observed greater ALFF abnormality of the PCu in slow-5 than in slow-4 in MCI patients [26]. A study also showed that the contributions of slow-4 and slow-5 to LFO amplitudes were different in brain regions such as the PCu, basal ganglia and thalamus in healthy subjects [23]. Moreover, the abnormalities in the extra-low frequency seemed to be greater than those in the other frequency bands for most brain regions in the current study. We speculate that the extra-low frequency band might be more sensitive than the other frequency bands in investigating regional brain activity in ADHD patients. Although the nature and meaning of these interactions remain unclear, these frequency-specific abnormalities would not be found using the traditional frequency bands [25]. A recent study suggested that the gradients of vertex-wise ReHo (2dReHo) along the divisions of the prefrontal cortex and posteromedial cortex revealed hierarchical organization within the two association areas [57]; such gradients might help us understand the neurophysiological meanings of ReHo and these frequency-specific differences. Additional correlation analyses of frequency-specific abnormality and clinical symptoms could aid us in further interpreting the clinical meanings of sub-frequency and ReHo and understanding the pathophysiology of ADHD.

4.3 The effects of the regression with nuisance covariates

A previous study indicated that high frequency RS-fMRI signals were strongly related to physiological (i.e., respiratory and cardiac) noise [21]. Recent work proposed that a regression with nuisance covariates was helpful in revealing the functional significant components in high frequency signals [58]. Therefore, to reduce the effects induced by head motion and non-neuronal BOLD fluctuations, we controlled for nuisance covariates, WM, CSF, GS and head motion. To assess the confounding effects on the results, we also conducted fMRI data processing in a regression without nuisance covariates. We found prominent differences between the results of these two processing strategies. The overall pattern of this regression appeared disorganized upon visual inspection, especially in the WM, OFC and temporal lobe. However, we found a relatively clearer pattern after performing the regression with the nuisance covariates. That is, the main effect of group pattern was primarily located in the DMN, and the interaction effect in the thalamus, SMA and occipital lobe appeared in the regression that included covariates. Thus, the results indicate that regressing out WM, CSF, GS and head motion reduces the influence of physiological noise on fMRI signals.

Moreover, Weissenbacher et al. [59] revealed that regression including GS as a covariate increased positive resting-state correlation and introduced a false-negative correlation. Thus, the authors recommended including WM, CSF, GS and head motion as covariates to maximize the specificity of positive resting-state correlation. Because there is controversy concerning the effect of GS on RS-fMRI data, we re-performed the data preprocess while regressing out WM, CSF and head motion (but not GS). We found that the results were roughly similar to the previous patterns. Specifically, we found significant main effects of group in the cerebellum, calcarine, MPFC and MFG and interaction effects primarily in the cerebellum, OIFG/OMFG, MPFC, SFG/MFG, SMA and lingual gyrus. Obviously, we found a main effect of group in the bilateral PCu when GS was controlled. The PCu findings did not hold when GS was not included as a covariate. The PCu is the core region of the DMN, which has frequently shown abnormalities in ADHD, as previously mentioned. Thus, a regression that includes GS as a covariate could result in a prominent between-group difference. A previous study indicated that such regression could denoise and decompose the signals aggregated over the network's regions [60]. Based on our results, the regression that controlled for GS did not result in a

substantial change to our findings and was helpful in investigating the neuromechanism of ADHD. However, Zuo et al. [61] suggested that GS reduced the test–retest reliability of ReHo; therefore, the current findings should be interpreted very carefully.

Several limitations of the current study should be taken into consideration. First, the children in the ADHD group had lower IQ scores than the healthy controls, and we did not control for IQ when performing the ANOVA. Given that IQ is a poorly specified latent variable that does not independently measure aptitude or predict more specific cognitive processes, the use of IQ as a matching variable or covariate might produce overcorrected and anomalous neurocognitive findings [62]. Therefore, the influence of IQ on the results remains unclear. Second, the patients in the current study were diagnosed as having one of three subtypes of ADHD (ADHD-I: 14, ADHD-HI: 1, ADHD-C: 15), and 13 patients had comorbidities (ODD: 12, CD: 1). Additional studies with larger and pure samples are needed to explore the differences among ADHD subtypes and to avoid the effect of comorbidity. Finally, in this study, the ADHD group only included boys. Investigations about girls with ADHD are needed to further examine gender differences in the physiopathologic mechanisms of ADHD.

5 Conclusions

In summary, the current study revealed lower ReHo in the DMN and complex abnormalities in the attention network in ADHD children. Importantly, the extra-low frequency band (<0.01 Hz) showed high sensitivity to abnormal spontaneous activity in ADHD children. The frequency-specific abnormalities in ADHD might provide insight into the abnormal functional integration between the individual neuronal processes of ADHD and advance our understanding of the pathophysiology of ADHD.

Acknowledgments This work was supported by the National Basic Research Development Program of China (2014CB846104), the National Natural Science Foundation of China (81371496, 30970802, 81101014) and the Program for New Century Excellent Talents in University (NCET-11- 0013). Dr. Zang is partly supported by the "Qian Jiang Distinguished Professor" Program.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Biederman J, Faraone SV (2005) Attention-deficit hyperactivity disorder. Lancet 366:237–248
2. Bush G, Valera EM, Seidman LJ (2005) Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry 57:1273–1284
3. Bush G (2010) Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology 35:278–300
4. Dickstein SG, Bannon K, Castellanos FX et al (2006) The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry 47:1051–1062
5. Durston S, van Belle J, de Zeeuw P (2011) Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biol Psychiatry 69:1178–1184
6. Rubia K, Halari R, Cubillo A et al (2011) Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naïve boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology 36:1575–1586
7. Valera EM, Faraone SV, Murray KE et al (2007) Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 61:1361–1369
8. Tian L, Jiang T, Wang Y et al (2006) Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 400:39–43
9. Sun L, Cao Q, Long X et al (2012) Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. Psychiatry Res 201:120–127
10. Castellanos FX, Margulies DS, Kelly C et al (2008) Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332–337
11. Zang Y, Jiang T, Lu Y et al (2004) Regional homogeneity approach to fMRI data analysis. NeuroImage 22:394–400
12. Liu H, Liu Z, Liang M et al (2006) Decreased regional homogeneity in schizophrenia: a resting state functional magnetic resonance imaging study. NeuroReport 17:19–22
13. Liu Z, Xu C, Xu Y et al (2010) Decreased regional homogeneity in insula and cerebellum: a resting-state fMRI study in patients with major depression and subjects at high risk for major depression. Psychiatry Res 182:211–215
14. Wu T, Long X, Zang Y et al (2009) Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp 30:1502–1510
15. Mankinen K, Long XY, Paakki JJ et al (2011) Alterations in regional homogeneity of baseline brain activity in pediatric temporal lobe epilepsy. Brain Res 1373:221–229
16. An L, Cao XH, Cao QJ et al (2013) Methylphenidate normalizes resting-state brain dysfunction in boys with attention deficit hyperactivity disorder. Neuropsychopharmacology 38:1287–1295
17. Cao Q, Zang Y, Sun L et al (2006) Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. NeuroReport 17:1033–1036
18. Cheng W, Ji X, Zhang J et al (2012) Individual classification of ADHD patients by integrating multiscale neuroimaging markers and advanced pattern recognition techniques. Front Syst Neurosci 6:58
19. Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929
20. Penttonen M, Buzsaki G (2003) Natural logarithmic relationship between brain oscillators. Thalamus Relat Syst 2:145–152
21. Cordes D, Haughton VM, Arfanakis K et al (2001) Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 22:1326–1333
22. Malinen S, Vartiainen N, Hlushchuk Y et al (2010) Aberrant temporal and spatial brain activity during rest in patients with chronic pain. Proc Natl Acad Sci USA 107:6493–6497
23. Zuo XN, Di Martino A, Kelly C et al (2010) The oscillating brain: complex and reliable. NeuroImage 49:1432–1445
24. Xue SW, Li D, Weng XC et al (2014) Different neural manifestations of two slow frequency bands in resting functional

magnetic resonance imaging: a systemic survey at regional, interregional, and network levels. Brain Connect 4:242–255
25. Yu R, Hsieh MH, Wang HL et al (2013) Frequency dependent alterations in regional homogeneity of baseline brain activity in schizophrenia. PLoS One 8:e57516
26. Han Y, Wang J, Zhao Z et al (2011) Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. NeuroImage 55:287–295
27. Yu R, Chien YL, Wang HL et al (2014) Frequency-specific alternations in the amplitude of low-frequency fluctuations in schizophrenia. Hum Brain Mapp 35:627–637
28. Yue Y, Jia X, Hou Z et al (2015) Frequency-dependent amplitude alterations of resting-state spontaneous fluctuations in late-onset depression. BioMed Res Int 505479
29. Gong Y, Cai T (1993) Manual of Chinese revised Wechsler intelligence scale for children. Hunan Atlas Publishing House, Changsha
30. Barkley RA (1998) Attention-deficit hyperactivity disorder: a clinical workbook, 2nd edn. Guilford, New York, pp 39–55
31. Yan CG, Zang YF (2010) DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. Front Syst Neurosci 4:13
32. Song XW, Dong ZY, Long XY et al (2011) REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6:e25031
33. Lv Y, Margulies DS, Villringer A et al (2013) Effects of finger tapping frequency on regional homogeneity of sensorimotor cortex. PLoS One 8:e64115
34. Van Dijk KR, Sabuncu MR, Buckner RL (2012) The influence of head motion on intrinsic functional connectivity MRI. NeuroImage 59:431–438
35. Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173
36. Ledberg A, Akerman S, Roland PE (1998) Estimation of the probabilities of 3D clusters in functional brain images. NeuroImage 8:113–128
37. Broyd SJ, Demanuele C, Debener S et al (2009) Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 33:279–296
38. Wilson TW, Franzen JD, Heinrichs-Graham E et al (2013) Broadband neurophysiological abnormalities in the medial prefrontal region of the default-mode network in adults with ADHD. Hum Brain Mapp 34:566–574
39. Cavanna AE, Trimble MR (2006) The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129:564–583
40. Cao X, Cao Q, Long X et al (2009) Abnormal resting-state functional connectivity patterns of the putamen in medication-naive children with attention deficit hyperactivity disorder. Brain Res 1303:195–206
41. Uddin LQ, Kelly AM, Biswal BB et al (2008) Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169:249–254
42. Helps S, James C, Debener S et al (2008) Very low frequency EEG oscillations and the resting brain in young adults: a preliminary study of localisation, stability and association with symptoms of inattention. J Neural Transm 115:279–285
43. Andrews-Hanna JR, Snyder AZ, Vincent JL et al (2007) Disruption of large-scale brain systems in advanced aging. Neuron 56:924–935
44. Luhmann CC, Chun MM, Yi DJ et al (2008) Neural dissociation of delay and uncertainty in intertemporal choice. J Neurosci 28:14459–14466
45. Cherkasova MV, Hechtman L (2009) Neuroimaging in attention-deficit hyperactivity disorder: beyond the frontostriatal circuitry. Can J Psychiatry 54:651–664
46. Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev 31:236–250
47. Rubia K, Smith AB, Halari R et al (2009) Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. Am J Psychiatry 166:83–94
48. Rubia K, Halari R, Christakou A et al (2009) Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philos Trans R Soc Lond B Biol Sci 364:1919–1931
49. Song X, Zhang Y, Liu Y (2014) Frequency specificity of regional homogeneity in the resting-state human brain. PLoS One 9:e86818
50. Fox MD, Snyder AZ, Vincent JL et al (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102:9673–9678
51. Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26:15–29
52. Fransson P (2006) How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 44:2836–2845
53. Gohel SR, Biswal BB (2015) Functional integration between brain regions at rest occurs in multiple-frequency bands. Brain Connect 5:23–34
54. Barry RJ, Clarke AR, Johnstone SJ (2003) A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 114:171–183
55. He BJ, Snyder AZ, Zempel JM et al (2008) Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. Proc Natl Acad Sci USA 105:16039–16044
56. Wang L, Saalmann YB, Pinsk MA et al (2012) Electrophysiological low-frequency coherence and cross-frequency coupling contribute to BOLD connectivity. Neuron 76:1010–1020
57. Jiang L, Xu T, Hou XH et al (2014) Toward neurobiological characterization of functional homogeneity in the human cortex: regional variation, morphological association and functional covariance network organization. Brain Struct Funct. doi:10.1007/s00429-014-0795-8
58. Yuan BK, Wang J, Zang YF et al (2014) Amplitude differences of high frequency fMRI signal between eyes open and eyes closed resting states. Front Hum Neurosci 8:503. doi:10.3389/fnhum.2014.00503
59. Weissenbacher A, Kasess C, Gerstl F et al (2009) Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. NeuroImage 47:1408–1416
60. Saad ZS, Gotts SJ, Murphy K et al (2012) Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect 2:25–32
61. Zuo XN, Xu T, Jiang L et al (2013) Toward reliable characterization of functional homogeneity in the human brain: preprocessing, scan duration, imaging resolution and computational space. NeuroImage 65:374–386
62. Dennis M, Francis DJ, Cirino PT et al (2009) Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. J Int Neuropsychol Soc 15:331–343