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Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI

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Abstract

In children with attention deficit hyperactivity disorder (ADHD), functional neuroimaging studies have revealed abnormalities in various brain regions, including prefrontal-striatal circuit, cerebellum, and brainstem. In the current study, we used a new marker of functional magnetic resonance imaging (fMRI), amplitude of low-frequency (0.01–0.08 Hz) fluctuation (ALFF) to investigate the baseline brain function of this disorder. Thirteen boys with ADHD (13.0 ± 1.4 years) were examined by resting-state fMRI and compared with age-matched controls. As a result, we found that patients with ADHD had decreased ALFF in the right inferior frontal cortex, left sensorimotor cortex, and bilateral cerebellum and the vermis as well as increased ALFF in the right anterior cingulated cortex, left sensorimotor cortex, and bilateral brainstem. This resting-state fMRI study suggests that the changed spontaneous neuronal activity of these regions may be implicated in the underlying pathophysiology in children with ADHD.

Keywords: Attention deficit hyperactivity disorder; Resting-state functional MRI; Amplitude; Low-frequency fluctuation; Spontaneous neuronal activity

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders in children and its core clinical symptoms include inattention, hyperactivity, and impulsivity [1]. Pathophysiological evidence has now been accumulated from structural and functional neuroimaging studies; for example, structural magnetic resonance imaging (MRI) showed that specific areas of the brain in ADHD subjects are smaller in size compared with normal controls, including the prefrontal lobe [2], caudate [3], cerebellum [2,4], and cerebellar vermis [4,5].

Functional neuroimaging techniques that have been utilized in the study of ADHD have mainly included single photon emission computed tomography (SPECT), positron emission tomography (PET) and blood oxygenation level dependent (BOLD) functional MRI (fMRI). Most SPECT and PET studies of ADHD have used the resting-state to measure cerebral blood flow (CBF) and found abnormalities in the striatum [6], frontal cortex [7], anterior cingulate cortex (ACC) [8], sensorimotor cortex (SMC) [7–10], and so on. There have been in excess of 10 previous documented BOLD fMRI studies of ADHD, some of

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which have reported hypofrontality [11–14] in ADHD subjects, whereas additional reports have hyperfrontality in other cases of this disorder [15,16]. Although two research groups used very similar tasks [16,17]; a Go–NoGo paradigm, an event-related design and the use of letters as a source of stimuli, the results of these two previous reports were quite different. Schulz et al. [16] described an increased level of activation in ADHD subjects in the left anterior cingulate cortex (ACC), but Tamm et al. [17] found decreased activation in ADHD subjects in the right ACC. The subtle differences in the assigned tasks between the two studies could partly account for the discrepancies. In the study by Schulz et al. [16], letter "X" was designated as the NoGo stimulus (17%) and "A" through "F" were the GO stimuli (83%). However, in the study by Tamm et al. [17], "X" (66%) and "B" (17%) were the GO stimuli and "A" (17%) was the NoGo stimulus. The former study utilized seven kinds of letters but the latter used three kinds. It therefore remains unclear to what extent the different types of letters account for the alternate findings from these two reports. To compare data obtained from different cognitive studies is certainly difficult and thus drawing clinically helpful conclusions from studies in which different cognitive tasks were used is quite challenging.

Resting-state fMRI has been developed as a new branch of this field. Biswal et al. [18] have shown previously that spontaneous low-frequency (<0.08 Hz) fluctuation (LFF) is highly synchronous among motor cortices. Such high synchrony has also been found within other functional systems in normal subjects [19]. Decreased LFF synchrony among remote brain areas has now been reported in many mental disorders such as early Alzheimer disease (AD) [20] and ADHD [21]. However, these studies had investigated LFF from the aspect of temporal synchronization, i.e., functional connectivity, but not from the aspect of regional activity during a resting-state. Although a result of abnormal functional connectivity between two remote areas is comprehensive and integrative, one could not draw any conclusion about which area is abnormal from such an examination. Regarding the amplitude of LFF (ALFF), Biswal et al. [18] found that ALFF was higher in grey matter than in white matter. In addition, Kiviniemi et al. [22] reported activation in the visual cortex due to low-frequency fluctuations at about 0.034 Hz using the power spectrum method, indicating that ALFF may be suggestive of regional spontaneous neuronal activity.

The purpose of our present study was to compare ALFF between ADHD and normal children. We hypothesized that ADHD children may have different ALFF in some brain areas, compared with the normal controls.

2. Methods

2.1. Subjects

The subject group comprised 13 boys with ADHD (13.0 ± 1.4 years) and 12 control boys (13.1 ± 0.6 years). The ADHD group subjects satisfied the diagnosis of ADHD based on both a structured diagnostic interview [23] with one parent and a teacher rating of DSM-IV. Also in this group, 10 children met the criteria for inattention-type and three children were found to be a combined-type of ADHD. Furthermore, 7 ADHD children also had comorbid learning disability and one had a mild form Tourette syndrome. In addition, 11 ADHD subjects were stimulant naive and a further two ADHD subjects received no stimulant medication for at least 48 h prior to the MRI scanning. For both ADHD and control subjects, other inclusion criteria included: (i) right-handedness, (ii) no history of neurological disease and no diagnosis of either schizophrenia, affective disorder, or pervasive development disorder and (iii) full scale Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R) [24] score of greater than 80. This study was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University. Informed consent was also obtained from the parent of each subject and all of the children agreed to participate in the study.

2.2. MRI Scanning

MRI data were obtained on a SIEMENS TRIO 3-T scanner in the Institute of Biophysics, Chinese Academy of Sciences. Each subject lay supine with the head snugly fixed by a belt and foam pads. The scanning sessions included: (i) localization, (ii) T2 anatomy (30 axial slices, thickness/gap = 4.5/0 mm, in-plane resolution = 256×256, FOV (field of view) = 200×200 mm, TR (repetition time) = 4000 ms, TE (echo time) = 29 ms), (iii) one resting-state and two task-state fMRI sessions. Task-state data were not presented in the current study. The resting-state data obtained from 11 children with ADHD and each of the control subjects were then used for discriminative analysis [25], based on the previously described regional homogeneity (ReHo) method [26], and also for functional connectivity analysis [21]. However, these methods are quite different from the current ALFF method. ReHo [26] and functional connectivity [21] analyses focus on the similarities of intra- and inter-regional time series, respectively, and ALFF measures the amplitude of regional activity. During the resting-state fMRI sessions, the subjects were asked to remain still as much as possible, keep their eyes closed and try not to think systematically. The order of the three sessions was randomized across subjects. The fMRI parameters used were: 30 axial slices, echo-planar

imaging pulse sequence, thickness/gap = 4.5/0 mm, in-plane resolution = 64 × 64, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm, 240 volumes (with exception of one subject who had only 200 volumes), (iv) diffusion tensor imaging session (not reported in the current study), and (v) 3D-T1 session covering the whole brain (176 sagittal slices, TR = 1730 ms, TE = 3.93 ms, thickness = 1.0 mm, no gap, in-plane resolution = 256 × 256, FOV = 240 × 240 mm, flip angle = 15°).

2.3. Data preprocessing

For the resting-state fMRI data, due to the fact that one of the subjects had only 200 volumes (lasting 6'40''), the first 200 of the 240 volumes (8 min) of each of the other 27 subjects were utilized for data analysis. The first 2 volumes were discarded for scanner calibration leaving 198 time volumes. Part of the data preprocessing was performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm), including slice timing, head motion correction (a least squares approach and a 6 parameter spatial transformation) and spatial normalization to the Montreal Neurological Institute (MNI) template (resampling voxel size = $3 \times 3 \times 3$ mm^3). The 3D-T1 images were also spatially normalized to the MNI template. Further data preprocessing was performed using AFNI (analysis of functional neuroimaging) software [27]. All images spatially normalized to the MNI template were then transformed to Talairach and Tournoux coordinates [28]. Subsequent data preprocessing included removal of linear trends and spatial smoothing (full width at half maximum = 8 mm Gaussian kernal).

2.4. Head motion calculation

After the head motion correction procedure, the magnitude of head motion at each time point for 6 parameters (3 for shift and 3 for rotation) was obtained for each subject. The averaged head motion parameter for shift and rotation was then calculated as follows:

$$\mathrm{Ms} = \sum(|sX_i - sX_{i-1}| + |sY_i - sY_{i-1}| + |sZ_i - sZ_{i-1}|)/197 \quad (1)$$

$$\mathrm{Mr}_{=} \sum(|rY_i - rY_{i-1}| + |rP_i - rP_{i-1}| + |rR_i - rR_{i-1}|)/197 \quad (2)$$

where Ms and Mr denote the averaged head motion parameter of shift and rotation, respectively. i denotes the time point of the time series, ranged 2–198. sX, sY and sZ denote the magnitude of shift in direction X, Y and Z, respectively. rY, rP and rR denote the magnitude of rotation in yaw, pitch and roll, respectively. The standard deviation (SD) of Ms and Mr across all subjects was then calculated. Subjects with head motion (Ms or Mr) exceeding +4 SDs were excluded from further analysis. Using this criterion, 2 ADHD subjects and 1 control subject were excluded and thus 13 boys with ADHD and 12 control boys were left.

2.5. ALFF analysis

ALFF analysis was performed using AFNI software [27] (see Fig. 1 for schematic illustration of this process). After preprocessing, the time series for each voxel was filtered (bandpass, 0.01–0.08 Hz) to remove the effects of very-low-frequency drift and high frequency noise, e.g., respiratory and heart rhythms [18,19]. Next, the filtered time series was transformed to a frequency domain with a fast Fourier transform (FFT) (parameters: taper percent = 0, FFT length = shortest) and the power spectrum was then obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component of the original time series in the time domain, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. For standardization purposes, the ALFF of each

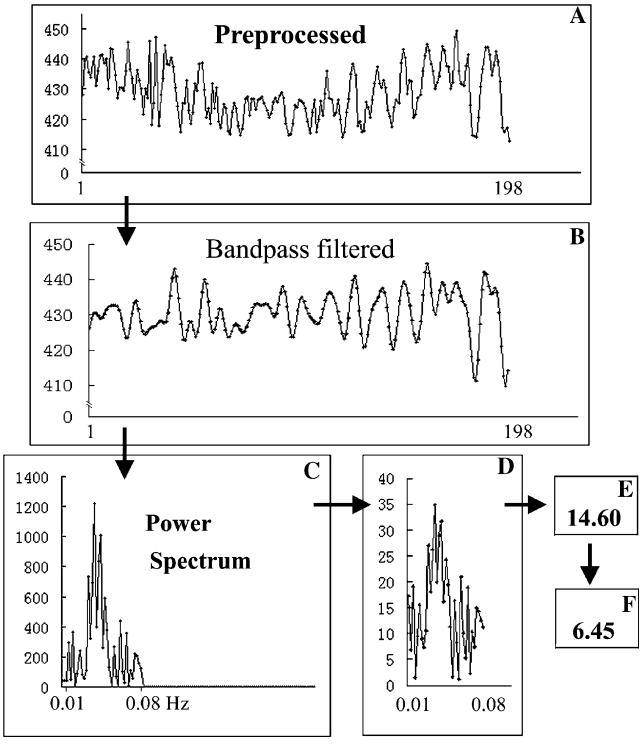

Fig. 1. Schematic illustration of the current ALFF analysis. The signal intensity is measured in arbitrary units. (A) The time course after preprocessing. (B) Band-filtered (0.01–0.08 Hz) time course. (C) Power spectrum using fast Fourier transformation. (D) Square root of the power spectrum between 0.01 and 0.08 Hz, i.e., ALFF. (E) Averaged ALFF across 0.01–0.08 Hz (14.60), the global mean ALFF (2.26) and the standardized ALFF (6.45).

voxel was divided by the global mean ALFF value. The standardized ALFF of each voxel should have a value of about 1 and this standardization procedure is analogous to that used in PET studies [29]. In our current study, the global mean ALFF was calculated only within the brain, i.e., background and other tissues outside the brain were removed. To achieve this, a set of spatially normalized 3D-T1 images of a normal subject were used to generate a brain-mask using MRIcro (Chris Rorden, http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html. See original Ref. [30]).

2.6. Statistics

Two-sample *t*-tests were used to examine the age and intelligence (IQ) differences between the two groups. For ALFF, a one-sample one-sided *t*-test was performed within each group to determine whether the ALFF differed from the value of 1 [29]. A two-sample *t*-test was performed to see the ALFF difference between the two groups. Voxels with a *P* value <0.01 (uncorrected) and cluster size >270 mm^3 (10 voxels) were considered to show significant difference between the two groups. Two-sample *t*-tests were also performed to assess the differences in head motion between the two groups. Moreover, a linear correlation was performed between the head motion values and ALFF of the peak voxels that showed the greatest ALFF group difference within a cluster. Linear correlations were also performed between the IQ and ALFF values of these peak voxels. Because the two groups showed significant differences on IQ as well as ALFF (see Section 3), a correlation between IQ and ALFF was performed for the ADHD group ($n = 13$) and control group ($n = 12$), respectively. However, these two groups were taken as a whole ($n = 25$) when a correlation between head motion and ALFF was performed, as the head motion measurement were not significantly different between the two groups (see Section 3).

3. Results

There were no significant age differences between the two groups ($T = 0.45$, $P = 0.660$). The ADHD subjects had significant lower IQ than the controls (ADHD = 99.0 ± 11.6; control = 118 ± 11.7; $T = 4.05$, $P = 0.0005$).

A one-sample *t*-test showed that the PCC/precuneus (PCC/PCu) had a significant higher standardized ALFF value than 1 in both the ADHD group (Fig. 2A and B) and control group (Fig. 2C and D). But it was clear that this analysis also showed some false positive results in some cisterns. A two-sample *t*-test showed significant difference between the two groups in some brain areas (Fig. 3 and Table 1). Unlike the results of one-sample *t*-test, however, all of the areas showing significant differences by the two-sample *t*-test were within the brain tissue except for one area in the right midbrain, where a few voxels of this cluster extended into the quadrigemina cistern (Fig. 3A, cluster number 2). Areas showing decreased ALFF in the ADHD group included the right inferior frontal cortex (IFC, Brodmann area (BA) 45), bilateral cerebellum and the vermis (Fig. 3 and Table 1). Some brain areas showed increased ALFF in ADHD subjects, including the right ACC (BA 24), left lateral cerebellum and left fusiform (these two areas were merged into one cluster), right inferior temporal gyrus (ITG, BA 37), left sensorimotor cortex (SMC) (BA 6) and bilateral brain stem (left midbrain and bilateral pons, Fig. 3 and Table 1).

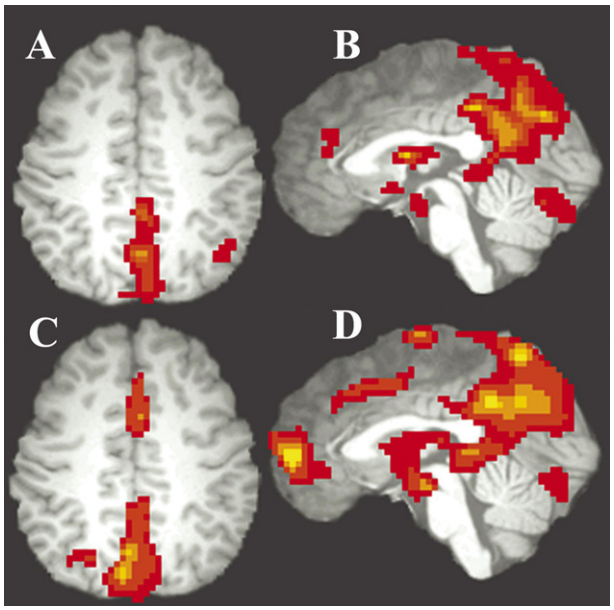

Fig. 2. Results of a one-sample *t*-test within group. (A and B) Control group with $T > 13.40$ and $P < 1.0. \times 10^{-7}$. (C and D) ADHD group with $T > 16.45$ and $P < 1.0. \times 10^{-10}$. (Note: that use of different thresholds for the two groups was merely for visual purposes. The statistical difference between groups is shown in Fig. 3 and Table 1).

There was no significant head motion differences between the two groups (shift: ADHD = 11.61E-2 ± 3.59E-2 mm, controls = 9.78E-2 ± 3.08E-2 mm, $T = 1.35$, $P = 0.19$; rotation: ADHD = 1.48E-3 ± 0.61E-3 degree, controls = 1.26E-3 ± 0.50E-3 degree, $T = 0.97$, $P = 0.34$). When the ALFF of the peak voxels within the clusters (Table 1 and Fig. 3B) was correlated to head motion, no significant correlation ($P \geqslant 0.09$, uncorrected for multiple comparisons) was found for either shift or rotation (Table 1). In addition, no significant correlation ($P \geqslant 0.06$, uncorrected for multiple comparisons) was found between the IQ and ALFF values in these peak voxels except for one peak voxel in the left pons in the ADHD group (see Table 1), where a significant correlation was reached $P = 0.03$ (uncorrected for multiple comparisons).

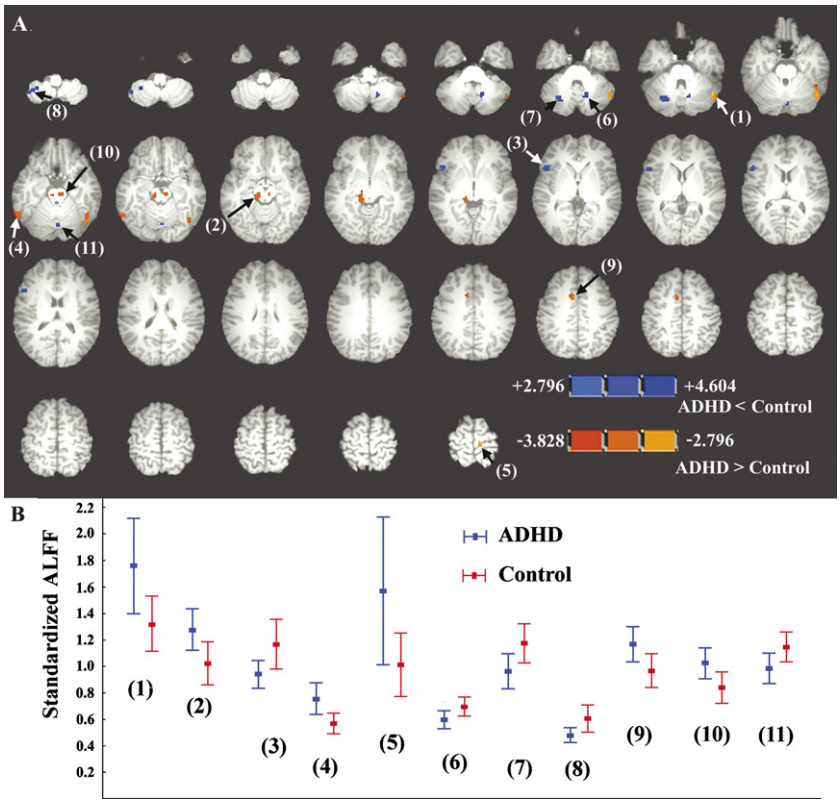

Fig. 3. ALFF differences between ADHD and control groups. (A) The differences map from $Z = -44$ to $Z = +66$ mm (every 4 mm) at the given threshold (cluster size > 270 mm^3, $|T| > 2.796$ and $P < 0.01$, uncorrected). Blue indicates that ADHD subjects had decreased ALFF compared with the controls and the yellow indicates the opposite. Left in the figure indicates the right side of the brain. (B) The mean and standard deviation of standardized ALFF at the peak voxels. The numbers (1)–(11) indicate the order of cluster size (from largest to smallest, see Table 1 for the corresponding brain areas).

4. Discussion

When attempting to interpret the differences that we found between boys with ADHD and controls, one primary question that arises is the nature of ALFF of the resting-state fMRI. In our current study, the results of the one-sample *t*-tests show that the PCC/PCu exhibited a standardized ALFF that was significantly higher than 1 (Fig. 2). This pattern is somewhat consistent with the default mode network proposed by Raichle et al. [29], which including PCC/PCu, medial prefrontal cortex and bilateral temporal–parietal areas, exhibits the highest metabolic rates of oxygen and glucose in the awake but resting-state. However, it is clear that our current one-sample *t*-test data also show more false positive areas (Fig. 2) than the results of previous PET studies (see figures of Ref. [29]). The locations of the brain that were associated with the *t*-test results between boys with ADHD and controls seemed to be more meaningful than the data generated within each group. Some investigators have attributed LFF to spontaneous neuronal activity (SNA) [31]. The electroneurophysiological studies have shown that SNA is of great physiological importance [32] and that many brain regions generate their own cyclical patterns that interact with those of other interconnecting regions [33]. However, the direct relationship between SNA observed by electrophysiological techniques and LFF observed by fMRI is not yet clear yet. By simultaneous electrophysiological recording and fMRI, Logothetis et al. [34] have found that task-induced BOLD signal changes correlated better to local field potential (LFP) than to single unit spiking, indicating that the BOLD response reflects the integration of input and intracortical processing other than spiking output. Such a combination is a good way of understanding the nature of LFF. In any case, based on the result of Logothetis et al. [34], one could presume that the LFF of resting-state fMRI should have the same underlying electrophysiological mechanism as the task-induced fMRI BOLD signal. Hence, it could be considered that ALFF reflects the extent of SNA. Brain diseases may exhibit abnormal local SNA and/or inter-regional SNA synchronization. The most comparable measure to the current ALFF might be resting PET. During the resting-state, both PET and ALFF measure the unconstrained, baseline state of mental activity. PET measures an averaged level of CBF or oxygen metabolism across a period of time, whereas ALFF

Table 1
Detailed information for clusters showing group ALFF differences at the given threshold (cluster size > 270 mm^3, $|T| > 2.796$ and $P < 0.01$, uncorrected) and the correlation coefficient of the ALFF of peak voxels with head motion and IQ

Volume	PV_X	PV_Y	PV_Z			BA	T	P	r Shift#	r Rotation#	rIQ ADHD†	rIQ Control†
2295	−49.5	−58.5	−18.5	L	Cbl, FG		−3.687	0.0012	0.24	0.31	−0.09	−0.17
1296	13.5	−25.5	−3.5	R	BS*a		−4.002	0.00055	0.15	0.10	−0.31	0.31
1215	46.5	19.5	5.5	R	IFC	45	3.823	0.00087	−0.10	−0.10	0.16	0.06
702	61.5	−52.5	−12.5	R	ITG	37	−4.604	0.00012	0.23	−0.02	0.50	−0.23
675	−10.5	−25.5	68.5	L	SMC	6	−3.197	0.004	−0.33	−0.32	−0.22	−0.19
648	−13.5	−58.5	−30.5	L	Cbl		3.362	0.0027	0.23	0.17	0.03	−0.09
594	28.5	−64.5	−21.5	R	Cbl		3.789	0.00094	−0.27	−0.35	−0.05	−0.26
540	46.5	−55.5	−45.5	R	Cbl		3.828	0.00086	−0.13	−0.07	0.48	0.12
486	7.5	13.5	38.5	R	ACC	24	−3.836	0.00084	0.22	0.15	−0.15	−0.41
432	−7.5	−19.5	−12.5	L	Pons		−4.058	0.00049	0.14	0.06	0.57	−0.11
378	−4.5	−67.5	−12.5		Vermis		3.397	0.0025	−0.01	−0.04	−0.36	−0.31

PV: peak voxel. *X*, *Y*, *Z*: coordinates in the Talairach–Tournoux atlas. BA: Brodmann area. *T*,*P*: *T* and *P* values from a *t*-test of the peak voxel (showing greatest statistical difference within a cluster), a positive *T* value means decreased ALFF in ADHD. *r*: correlation coefficient. L, R: left and right. Cbl: cerebellum. FG: fusiform gyrus. BS: brain stem, including midbrain and pons. IFC: inferior frontal cortex. ITG: inferior temporal gyrus. SMC: sensorimotor cortex. ACC: anterior cingulate cortex. *a: The gravity of this cluster was centered in midbrain but the peak voxel extended to the quadrigemina cistern. #: All the *P* values $\geqslant 0.09$ ($n = 25$). †: Correlation was performed for the ADHD group ($n = 13$) and control group ($n = 12$), respectively. Only the correlation coefficient of 0.57 corresponds to a *P* value of 0.03 (uncorrected for multiple comparison). All others correspond to $P \geqslant 0.06$.

measures the deviation, rather than the mean, of the BOLD signal. The relationship between ALFF and CBF still needs further investigation.

In our current study, we found significant ALFF differences between ADHD and control children. Some areas of the brain showed decreased ALFF in the ADHD group, including the right IFC (BA 45), bilateral cerebellum and the vermis. Areas showing increased ALFF in ADHD comprised the ACC (BA 24), left lateral cerebellum and left fusiform, right ITG (BA 37), left SMC (BA 6) and bilateral brain stem (Fig. 3 and Table 1). Some, but not all, of these results are consistent with previous findings in ADHD studies.

Based on a broad review of neuroimaging studies, some investigators [35] concluded that a deficit in frontal-striatal circuitry might be the most critical determinant for ADHD pathophysiology. Abnormal activity in the striatum of ADHD children has been reported by many functional neuroimaging studies, including resting-state SPECT [6], T2-relaxometry MRI [36], magnetic resonance spectroscopy [37], and task-state fMRI [11–13,38]. However, in our present study, we did not find significant ALFF differences in the striatum between the two groups, which may be partially due to a relatively weak fMRI signal to noise ratio in basal ganglia in resting-state fMRI. Previous reports of a prefrontal deficit in ADHD are not very consistent. In previous task-state fMRI studies, hypofunction in the right IFC [11–13,16] has been reported more frequently than hyperfunction [15]. A decreased prefrontal activity in children with ADHD found in our current study may also indicate prefrontal hypofunction, which would appear to support hypofrontality in ADHD.

Dorsal ACC (dACC, BA 24/32) has been reported to be involved in many cognitive processes such as performance monitoring, target selection, response inhibition, and reward [39]. Compared to other cortical areas, dACC can be circumscribed easily and, hence, can be readily compared across different studies. A few functional neuroimaging studies have found ACC abnormalities in ADHD. In a task-state, decreased activity has been found in ACC by PET [40] and fMRI [13,17]. However, one fMRI study [16] has found increased ACC activity in ADHD subjects compared with matched controls. In the resting-state, Langleben et al. [8] previously used SPECT and reported that methylphenidate reduces ACC activity in ADHD subjects. Their data may thus implicate a higher level of CBF in ACC in ADHD subjects before methylphenidate administration, compared with normal controls. Using resting-state fMRI, our current study found more activity in the ACC of ADHD subjects than the controls (Fig. 3 and Table 1) being consistent with that of Langleben et al [8]. Based on these results, we speculate that decreased ACC activity in the task-state may result from increased spontaneous neuronal activity in ADHD subjects. Task-state activities are usually defined as a signal change from the resting-state or control state to a task-state, whereas the resting-state measures the baseline activity. Therefore, a task-state is a more complicated measurement. Moreover, the relatively long resting-state used in PET, SPECT and our current study may be somewhat different from the shorter resting states utilized in activation fMRI studies, particularly when an event-related fMRI design was used. Thus, a direct comparison of the results obtained in a resting-state and a task-state should be performed with caution.

In neuroimaging research on ADHD, increasing attention has now been focused on the cerebellum. A few structural MRI studies have found a smaller cerebel-

lum volume in ADHD subjects [2,41]. A reduced volume of the posterior–inferior lobe of vermis was also reported by two independent MRI studies [4,5] and cerebellar white matter impairment was described following the using diffusion tensor MRI in ADHD [42]. During the resting-state, it was also previously found that methylphenidate could increase the CBF in the vermis of ADHD subjects by using SPECT [9] and T2-relaxometry MRI [43]. The findings of these two studies might indicate that ADHD subjects who were not receiving methylphenidate had abnormal decreased CBF in the vermis. Our present study shows reduced spontaneous fluctuation in the vermis and bilateral cerebellum (Fig. 3 and Table 1). All of these structural and functional imaging results indicate that cerebellar dysfunction may also play an important role in the pathology of ADHD.

Our current study has demonstrated increased ALFF in the left SMC (BA 6) (Fig. 3 and Table 1). Some of the previous PET and SPECT studies have also reported dysfunction of the SMC in ADHD cases during the resting-state. At least four such reports, for PET [9] and SPECT [7,8,10], have shown very similar results in a similar way i.e., methylphenidate can reduce CBF in the SMC. Together with our current data, all of these resting-state functional imaging results indicate that the sensorimotor area may exhibit hyperfunction in ADHD. The effects of methylphenidate suggests 'an inhibition of function of these structures, seen as clinically less distractibility and decreased motor activity during treatment' [10].

For the brain stem, the spatial resolution of fMRI is relatively low and the fMRI signal is also sensitive to the stronger physiological pulsation near the skull base. Despite these limitations, fMRI has been used to study brain stem function [44]. We have performed fMRI and found that ALFF significantly increases in the brain stem (right midbrain and bilateral pons) of ADHD subjects compared with the controls (Fig. 3 and Table 1). Lou et al. [10] reported earlier that methylphenidate can increase the CBF in the midbrain of ADHD subjects which appears inconsistent with our present findings. Ernst et al. [45] found that dopa decarboxylase activity was elevated in the right midbrain of ADHD children but the relationship between the elevated dopa decarboxylase activity and the decreased extracellular dopamine level remained unclear. Hence, the relationship between the increased ALFF, probably indicating increased SNA, found in our current study and the density of dopaminergic transmitters is likely to be more complicated. In addition, in order to repeat our present findings of the brain stem in future studies, the procedure should be quite carefully designed, for example with higher spatial resolution or by observing the effects of methylphenidate on ALFF.

Head motion is relatively more problematic for children than adults during fMRI, particularly for ADHD children. However, in our current study, we did not find significant differences in head motion between ADHD children and controls ($P = 0.19$ for head shift, $P = 0.34$ for rotation). Moreover, the magnitude of head motion was not significantly correlated to ALFF ($P \geqslant 0.09$. See Table 1) but head motion correction and high-pass filtering should reduce the head motion effects upon ALFF. However, more limited head motion should yield better and more reliable results.

Some of the methods used in our current study will require improvement and some of the current findings will need to be clarified in future studies. Firstly, we used a low sampling rate (TR = 2 s) and were not able to simultaneously record cardiac rate due to technical limitations. We therefore could not resolve the bias generated by the cardiac rate (usually more than 1 Hz) [19] though we do not believe that our calculated between-group differences are attributable to heart rate difference between ADND and normal controls. Secondly, multiple comparison correction is used not for the difference between the two groups. One way for increasing statistical power after multiple comparison correction would be to use a more circumscribed mask that could be obtained, for example, by removing white matter and cerebrospinal fluid, or removing regions of no interest by an established threshold. However, these procedures are not appropriate for an initial study such as the current one. Future studies could focus on a few specific regions of interest and in such instances, the statistical significances of group difference would be more meaningful after multiple comparison correction. In addition, a larger group of subjects would also increase the statistical power of the study. Thirdly, the correlation of IQ with ALFF is not interpreted in our present study. In view of the fact that children with ADHD generally display a lower IQ, the use of IQ as a covariate in ADHD studies is still a matter of some debate. It may depend on the specific research question [46]. It should however be clarified in any future study that to what extent IQ could account for the ALFF difference between ADHD and control groups. Finally, the mixed subtypes in the ADHD group in our current study may have confounding effects on the results and future studies that compare subtypes in ADHD would likely assist in our understanding of the underlying mechanisms.

In conclusion, in our present study, most of the findings of abnormalities in ADHD subjects, including decreased ALFF in the right IFC and the cerebellum and increased ALFF in ACC, left SMC and bilateral brain stem, are consistent with previous reports. This resting-state fMRI study thus suggests that the abnormal spontaneous activity of these regions may implicate the underlying pathophysiology in children with ADHD. The relationship between abnormal ALFF and the behavioral performance of ADHD therefore needs to be clarified in future studies.

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