



## Abnormal spontaneous brain activity in medication-naïve ADHD children: A resting state fMRI study

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### ABSTRACT

Abnormal baseline brain functional connectivity in attention-deficit/hyperactivity disorder (ADHD) has been revealed in a number of studies by using resting-state functional MRI (rfMRI). The aim of this study was to investigate the spontaneous frontal activities in medication-naïve ADHD boys using the rfMRI derived index, amplitude of low-frequency fluctuation (ALFF). In total 17 ADHD boys and 17 matched controls were recruited to undergo rfMRI scan on a 3.0 T MRI system. For each subject, six oblique slices covering the frontal areas were acquired with a rapid sampling rate (TR = 400 ms). Functional images were processed in AFNI for calculation of ALFF and then group comparison was performed using voxel-based *t*-test. With a corrected threshold of  $p < 0.05$  determined by AlphaSim, we found that in comparison with controls, ADHD patients demonstrated higher ALFF values in the left superior frontal gyrus and sensorimotor cortex (SMC), and lower ALFF values in the bilateral anterior, middle cingulate and the right middle frontal gyrus (MFG). Significant correlations were found between patients' WSCT measures and the peak ALFF located in the right MFG ( $r = 0.69$ ,  $p = 0.02$ ), and the left SMC ( $r = 0.65$ ,  $p = 0.03$ ). Our results revealed abnormal frontal activities at resting state associated with underlying physiopathology of ADHD, and suggested the ALFF analysis to be a potential approach in further exploration of this disorder.

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Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder worldwide, affecting 5–10% of school-age children. Convergent data from genetic, neurochemical [31] and neuropsychological [24] studies have suggested fronto-striatal abnormalities as the likely cause of this disorder.

Imaging studies have revealed structural abnormalities in ADHD brain, such as global [5] or regional tissue volumetric reduction [18], and widespread cortical thinning [17]. Functional abnormality in ADHD brain has also been revealed earlier by studies using either positron emission tomography (PET) [32] or single photo emission computed tomography (SPECT) [16]. With the application of functional magnetic resonance imaging (fMRI), prefrontal hypofunction associated with motor control has been demonstrated in ADHD

adolescents [19]; however, contradictory finding, i.e. enhanced frontostriatal activation during inhibition, has been observed in adolescents who had been diagnosed as ADHD during childhood [20].

Resting-state fMRI (rfMRI), since first proposed by Biswal et al. [1], has been applied to studies of various brain disorders. It does not require the subject to perform any task, thus greatly simplifies the fMRI procedure. A number of rfMRI studies have been carried out on ADHD either in children [2,4,9] or adults [8,28]. Increased resting-state functional connectivity (FC) with the dorsal anterior cingulate cortex (ACC) in bilateral ACC, thalamus, cerebellum, insula and brainstem has been revealed in ADHD adolescents [27]. Sonuga-Barke and Castellanos have proposed a default mode interference hypothesis which postulates that patterns of spontaneous brain activity in ADHD cause attention lapses when they remain unattenuated following the transition from rest to periods of active task processing [23]. Their further work revealed decreases in the FC between ACC and precuneus/posterior cingulate regions [6]. These rfMRI studies were focused on FC among different brain areas. As such, it is difficult to pinpoint

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which area is responsible for the observed connectivity alterations.

The first rfMRI study by Biswal et al. [1] has suggested the amplitude of the spontaneous low-frequency fluctuation (ALFF) of the blood oxygen level dependent (BOLD) signal to be an indicator of regional spontaneous neuronal activity. The sensitivity of ALFF has been validated in an eye-open/eye-close comparison rfMRI study [29], and it has also been applied to investigation of brain function in ADHD patients [33]. The aim of this study was to investigate the spontaneous brain activities in frontal lobe in medication-naïve ADHD boys by using the ALFF measure derived from rfMRI signal.

Originally 21 boys with ADHD and 20 healthy controls were recruited and tested by experienced pediatric psychiatrists. Finally 17 ADHD boys ( $7.510.03 \pm 1.96$  years) and 17 age- and education-matched healthy male controls ( $9.73 \pm 1.57$  years) were met all the inclusion criteria and left for results presentation. They were primary school students of 2–6 grade and all belong to the Chinese Han ethnic group. Inclusion criteria include: (1) right handedness; (2) no history of schizophrenia, affective disorder, Tourette disorder or any other neurological and psychiatric disorders besides ADHD; (3) no evidence of severe language development delay and communication problems; and (4) full scale intelligence quotient (IQ) score according to the Wechsler Intelligence Scale for Children Revised in China (C-WISC) [10] higher than 75. ADHD was diagnosed according to the Clinical Diagnostic Interviewing Scale based on DSM-IV [30]. ADHD subjects were predominantly inattention type (ADHD-I) (five patients) or combined type (ADHD-C) (12 patients); stimulants-naïve. Boys with hyperactivity disorder with comorbid conduct disorder or oppositional defiant disorder were not excluded. Six had comorbid oppositional defiant disorder. Neuropsychological tests using Achenbach's Child Behavior Checklist (CBCL), Conners' Parent Symptom Questionnaire (PSQ) and Wisconsin Card Sorting Test (WCST) were also performed for ADHD patients, among which WCST were only completed in 11 subjects. This study was approved by the Ethics Committee of the hospital, and written informed consent was obtained from guardians of all participants.

MRI scanning was carried out on a 3.0T scanner (GE EXCITE, Milwaukee, USA). Subjects were asked to close eyes, and lay supinely with their heads snugly fit to foam pads to reduce head motion. T1-weighted images were obtained in six oblique coronal slices covering the frontal area using a spin-echo sequence (slice thickness/gap = 5/1 mm, TR/TE = 2382/25 ms, flip angle (FA) = 90°, matrix = 512 × 512, field of view (FOV) = 24 cm × 24 cm. Functional MRI data was acquired by using an echo-planar sequence whose slice positions were the same with T1 images (Fig. 1). Other parameters for rfMRI: TR/TE = 400/30 ms, FA = 30°, matrix = 64 × 64, FOV = 24 cm × 24 cm, total volumes = 1000. A high sampling rate (TR = 400 ms) was used to decrease the physiological (e.g., respiratory and cardiac) confounding effects on the BOLD signal. The whole brain volume scan was acquired using a 3D spoiled gradient-recalled echo sequence (156 axial slices, matrix 512 × 512, TR/TE = 8.5/3.4 ms, FA = 12°, FOV = 24 cm × 24 cm, thickness/gap = 1/0 mm) for data processing. The total scan time of the trial was about 15 min. After scanning, all subjects confirmed that they did not fall asleep during the scan.

Imaging data processing was performed in AFNI (Analysis of Functional NeuroImages, NIMH). Data acquired in the first 16 s were discarded to avoid transient MR signal changes and to allow subjects to get used to the scanning noise. After slice timing and head motion correction, data from 4 patients and 3 controls were discarded because of excessive head motion (>3 mm in displacement or >3° in rotation), thus 17 patients and 17 controls were left for further analysis. The rfMRI and T1 image were manually registered to 3D image, followed by normalization.

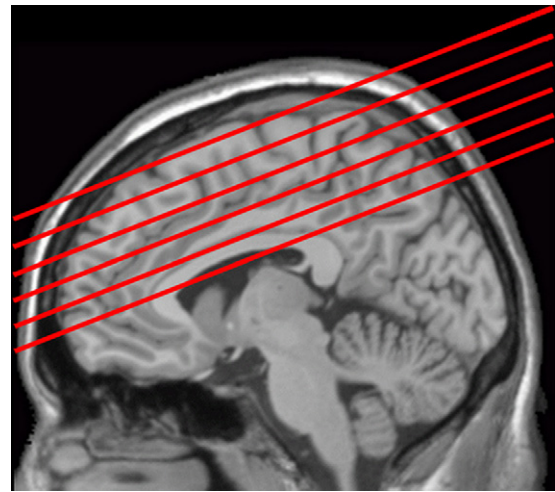


Fig. 1. Schematic location of the six oblique slices.

After band-pass filtering (0.01–0.08 Hz) and linear-trend removal, the time series were transformed into frequency domain using fast Fourier transformation (FFT). Then the spectrum in frequency domain was square-rooted and averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. For detailed description of ALFF calculation, please refer to Yang et al. [29]. ALFF maps were then spatially normalized, resampled (3 mm × 3 mm × 3 mm) and smoothed (FWHM = 6 mm). For normalization purposes, a brain mask was obtained from the intersection of the brain of all subjects' normalized T1 images, and the ALFF of each voxel in an individual subject was divided by his mean ALFF value within the mask.

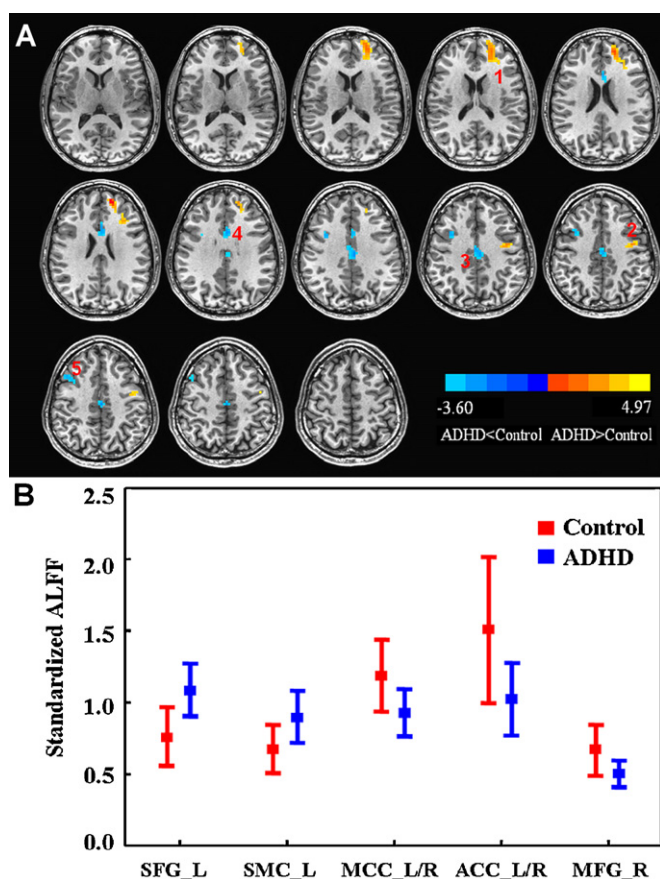
Group differences in age, IQ and ALFF were examined using 2-sample *t*-tests. For ALFF comparison, a combined threshold of  $p < 0.005$  and a minimum cluster size of 486 mm<sup>3</sup> was used, which resulted into a corrected threshold of  $p < 0.05$  determined by AlphaSim program in AFNI. Linear correlative analyses were performed between the neuropsychological measures of ADHD patients and ALFF values of the peak voxels within clusters. Head motion parameters between the two groups were also compared with 2-sample *t*-test, and a linear correlation was performed between head motion parameters and the peak ALFF.

Age was not different between patients and controls, but the IQ of patients ( $89.8 \pm 10.3$ ) was significantly lower than controls ( $117.5 \pm 13.6$ ;  $p < 0.001$ ). Compared to controls, medication-naïve ADHD patients demonstrated higher ALFF values in the left superior frontal gyrus (SFG) and left sensorimotor cortex (SMC), and lower ALFF values in the bilateral ACC, middle cingulate cortex (MCC), and right middle frontal gyrus (MFG) (Fig. 2A). The peak voxels within those clusters showing significant group differences are shown in Fig. 2B and Table 1.

No significant correlations between IQ, CBCL, PSQ derived measures and peak voxel ALFF values were found. Among the 11 ADHD subjects who completed WCST, significant correlations were found between their perseverative errors and the peak ALFF located in the right MFG ( $r = 0.69$ ,  $p = 0.02$ ), and between the categories achieved and the peak ALFF located in the left SMC ( $r = 0.65$ ,  $p = 0.03$ ) (Table 1).

No significant group difference in head motion was found (whole shift: control =  $106.6 \pm 7.9$ , patients =  $104.5 \pm 8.4$ ,  $p = 0.39$ , whole rotation: controls =  $104.6 \pm 9.0$ , patients =  $105.3 \pm 8.7$ ,  $p = 0.45$ ), and the head motion was also not correlated with the peak ALFFs ( $p < 0.05$ ).

In this study, significant altered ALFF was observed in medication-naïve ADHD boys relative to controls, including higher ALFF in the left SFG and SMC (specifically in the precentral gyrus)



**Fig. 2.** ALFF differences between medication-naïve boys ADHD and control groups. (A) 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. Numbers 1–5 denote the location of the five clusters SFG.L, SMC.L, MCC.L/R, ACC.L/R and MFG.R, as listed in Table 1, respectively. (B) The mean and standard deviation of standardized ALFF at the peak voxels in medication-naïve boys and normal controls. The x-axis indicates the clusters in which the peak voxel located. For the full name of the abbreviations, please refer to the legend for Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

areas, and lower ALFF in bilateral ACC, MCC and right MFG. The increased regional ALFF as well as the reduced ALFF in right MFG observed were similar to previous ADHD studies [3,14–16,21,22]. The increased ALFF in SMC areas in ADHD children were also observed by Zang et al. [33] previously. However, the ALFF decrease in ACC and MFG we found were not reported by them, meanwhile,

**Table 1**  
Brain regions showing ALFF difference between two groups.

Brain regions	Volume (mm <sup>3</sup> )	BA	Peak voxel			
			x	y	z	T
ADHD > control						
SFG.L	3321	9	13.5	-46.5	26.5	4.97
SMC.L*	648	6	37.5	7.5	35.5	3.71
ADHD < control						
MCC.L/R	1539	6	1.5	19.5	41.5	-3.60
ACC.L/R	945	24/33	1.5	-7.5	29.5	-3.51
MFG.R**	891	6/9	-31.5	-4.5	32.5	-3.39

BA, Brodmann area; x, y and z are location of peak voxels in the Talairach–Tournoux coordinate; SFG, superior frontal gyrus; SMC, sensorimotor cortex; MCC, middle cingulate cortex; ACC, anterior; MFG, middle frontal gyrus.

\* Significant correlations between ALFF at this peak voxel with numbers of categories achieved.

\*\* Significant correlations between ALFF at this peak voxel with numbers of perseverative errors.

a decrease in ALFF in the right inferior frontal gyrus (IFG) in their study was not shown in our study. The discrepancies could be related to the different ADHD patient mixture in the two studies. In our study, the medication-naïve ADHD boys included five ADHD-I patients and 12 combined type (ADHD-C), but in contrast, they recruited ten ADHD-I and three ADHD-C patients, among which two were not stimulant-naïve. Additionally, compared with Zang et al. [33], being specifically interested in the abnormal frontal function, we focused our fMRI scanning on the frontal lobe, which allowed a higher sampling rate to be used in our study (0.4 s compared to 2 s).

The prefrontal cortex has been assumed to be the main disturbed brain regions in ADHD which was supported by imaging studies [5,12]. Dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex are thought to support vigilance, selective and divided attention, attention shifting, planning, executive control, and working memory. An fMRI study has reported increased activation in the DLPFC and considered that as a compensatory mechanism in ADHD children when performing reorienting task [14]. Smith et al. also found increased superior frontal activation in their fMRI study [22]. The higher ALFF in left SFG we observed in patients indicated that the resting state regional activity was also increased in DLPFC. We also observed relatively increased ALFF in the right superior frontal area which did not survive the multi-comparison correction. Whether this result indicated a compensatory mechanism needs further investigation.

Dysfunction of the SMC in ADHD during the resting-state has been also reported by previous studies. Three reports, by using PET [21] or SPECT [15,16], have shown very similar results, i.e., administration of methylphenidate can reduce CBF in the SMC, according to which we can speculate that the SMC CBF was abnormally higher in their ADHD subjects before treatment. Our results, in line with Zang et al.'s finding, confirmed the resting state hyperfunction of SMC (BA6) in ADHD.

Dorsal ACC is functionally involved in many cognitive processes such as performance monitoring, target selection, response inhibition, and reward. In ADHD, of which such functions disrupted, ACC abnormalities have been found in a few imaging studies. However, the previous findings were not consistent in terms of the changing pattern of ACC function. Two studies, one with task-fMRI [14] and another with rfMRI [2], have found decreased ACC activity in ADHD children. Especially the later one, which also examined medication-naïve ADHD boys, revealed quite similar results to our current findings. However, in the above-mentioned SPECT study [15], higher regional CBF was reported not only in motor areas, but also in the ACC in ADHD subjects, compared with normal controls. As well as in the rfMRI study by Zang et al. [33], the ACC of ADHD boys showed higher spontaneous activity than the matched controls. The discrepancies, on one hand, could be partially attributed to the differences between subjects in each study; on the other, direct comparison between results derived from different approaches to measuring brain function is difficult to make. It is hampered by the current lack of clear theory of the relationship between brain function measured by ALFF and information obtained by other means, such as CBF measurement, or task-fMRI. Whether the inconsistency is related to the ADHD subtype or other factors need to be further studied.

The MCC cluster we identified (Fig. 2A), is quiet close to the dorsal ACC area, and traditionally considered as a part of the anterior cingulate cortex. Functionally it's close to the anterior part of cingulate as well, and has been observed with abnormal function in ADHD. For example, Tamm et al. have performed Go/No-Go task fMRI on ADHD patients and found hypofunction in ACC/MCC extending to the supplementary motor area compared with controls [26]. In another fMRI study by the same group employing a visual oddball task [25], ADHD group showed less MCC activation

than control group for the oddball versus standard events condition. Thus we can speculate that the two clusters within ACC and MCC in our study plays similar role in the ADHD cognitive dysfunction.

Some previous studies have demonstrated that the activation of MFG is associated with cue processing [11,13]. Processing of the cue could increase phasic arousal or even the ability to prepare for a motor response in advance [7]. Using fMRI, a recent study reported decreased neural activity in middle frontal gyrus that associated with poorer phasic alertness [3]. Currently, we also observed decreased neural activity in the right middle frontal gyrus of ADHD children relative to controls, although the mechanisms leading to these changes were not investigated.

Head motion is possibly more problematic for children than for adults during fMRI scanning, especially for children with ADHD. In our current study, neither significant group differences in head motion nor correlation between head motion and peak ALFF was observed. Moreover, removing of head motion effect and high-pass filtering were used in data processing that reduced the head motion effects upon ALFF, so the head motion was unlikely to be a contributor to the significant ALFF differences. However, more limited head motion should yield more reliable results.

In our subjects, the ADHD boys had lower IQ than that of controls; however, in view of the fact that ADHD children generally display a lower IQ, and not being a key character of ADHD, we did not include IQ as a covariate in group comparison. We did not reveal any significant correlation between IQ and peak voxel ALFF in either controls or ADHD groups. Similar to us, Zang et al.'s study also failed to find out such a correlation [33]. Thus we can speculate that the IQ would not likely to contribute much to the observed ALFF differences, though it may correlate with ALFF in certain intelligence-related cerebral regions. Anyway, it should be clarified in future study that how IQ interact with ALFF difference between ADHD and control groups.

There are several limitations in this study. Firstly, the mixed ADHD subtypes may have confounding effects on the results. Future studies that compare subtypes in ADHD would likely assist in our understanding of the underlying mechanisms. Secondly, standardized ALFF maps were obtained by dividing ALFF of each voxel by the mean ALFF value within a mask; however, our mask only covered limited brain areas, so the standardization procedure was not optimized. Thirdly, although significant correlations were found between WSCT measures and frontal ALFF, the WSCT were only completed in 11 patients, and, ALFF were not correlated with hyperactivity indices from CBCL, PSQ. Further investigation should be focused on the relationship between neurobehavioral deficits and abnormal spontaneous prefrontal activity.

In summary, we have demonstrated generally consistent findings with previous studies of ADHD, namely, the medication-naïve ADHD boys showed increased ALFF in the left SFG and SMC area and decreased ALFF in the cingulate cortex and right middle frontal lobe as compared to the control group. Our results provided reinforced evidences for the frontal dysfunction in ADHD, and more importantly, validated the feasibility of using resting-state ALFF measurement with higher sampling rate in exploring pathologic mechanisms in this disorder.

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