Abnormal Brain Activity in ADHD: A Study of Resting-State fMRI

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Abstract. The prevalence rate of ADHD varies from age to age. To better understand the development of ADHD from childhood to adolescence, different age groups of ADHD from large dataset are needed to explore the development pattern of brain activities. In this study, amplitude of low frequency fluctuation (ALFF), fractional amplitude of low frequency fluctuation (fALFF) and regional homogeneity (ReHo) were extracted from resting-state functional magnetic resonance imaging (rs-fMRI) of both ADHD subjects and typical developing (TD) subjects from 7 to 16 years old. The result showed that the different areas mainly appear at the bilateral superior frontal cortex, anterior cingulate cortex (ACC), precentral gyrus, right superior occipital lobe, cerebellum and parts of basal ganglia between all ADHD subjects and all TD subjects. Besides, compared with TD, there were different brain activity patterns at different ages in ADHD, which appear at the left ACC and left occipital lobe. The result can inspire more studies on comparisons between functional connectivity methods.

Keywords: Rs-fMRI · ADHD · Brain development

1 Introduction

Attention deficit hyperactivity disorder (ADHD) is generally considered to be a neurodevelopmental disorder with high incidence in childhood [1, 2]. It is mainly characterized by lack of attention, excessive activity (restless in adult), or difficulty controlling behavior which is not appropriate for a person's age [3]. It was estimated that the prevalence of ADHD in pre-school children (3–6 years old) in Europe is 1.8–1.9% [4]. Although there is no global consensus, meta-regression analyses have estimated the worldwide ADHD prevalence at between 5.29% and 7.1% in children and adolescents, and at 3.4% in adults [5–7]. In addition, about 30–50% of people diagnosed with ADHD in childhood continue to have symptoms into adulthood and about 2–5% of adults also have the symptoms [8]. Since the incidence of ADHD varies between ages, in order to understand the development of ADHD from childhood to adolescence, it is necessary to explore the difference patterns of regional brain activities between ADHD subjects and typical developing (TD) subjects from different age groups.

Y. Zeng et al. (Eds.): BI 2017, LNAI 10654, pp. 181–189, 2017.
https://doi.org/10.1007/978-3-319-70772-3_17

Functional magnetic resonance imaging (fMRI) has been widely used to measure brain activities in-vivo. Compared to the task-related fMRI, resting-state fMRI (rs-fMRI) does not require subject to perform any task, which greatly simplifies the fMRI procedure for patients with difficulty to accomplish certain tasks. Brain activity could be characterized by different measurements, such as amplitude of low frequency fluctuation (ALFF), fractional amplitude of low frequency fluctuation (fALFF) and regional homogeneity (ReHo). Since Zang et al. [9] applied ALFF to probe the abnormal spontaneous neuronal activities of ADHD patients, ALFF has been widely used in the studies of various mental diseases, such as schizophrenia [10, 11], autism spectrum disorder [12], attention deficit hyperactivity disorder [13]. However, some researchers found that ALFF of ADHD patients increased abnormally in some brain areas but the energy consumption of these regions did not increase correspondingly, which was likely to be caused by noise. Therefore, Zou et al. [14] proposed fALFF to reduce the abnormal value in ALFF. At the same time, Zang et al. [15, 16] firstly proposed the regional homogeneity approach and explored the functional abnormalities of Parkinson's patients using ReHo. Subsequently, many studies have validated the feasibility of ReHo in the analysis of fMRI data from multiple aspects [17, 18].

The different brain activities between ADHD and TD have been identified in previous studies. For example, comparing the value of ALFF between 17 ADHD boys (7.51 $\pm$ 1.96 years old) and 17 matched controls (9.73 $\pm$ 1.57 years old), Yang et al. [13] found that ADHD showed higher ALFF in the left superior frontal gyrus and sensorimotor cortex (SMC) as well as lower ALFF in the bilateral anterior, middle cingulate and the right middle frontal gyrus (MFG). Using ALFF and ReHo on a smaller sample, in contrast to 12 controls (12.5 $\pm$ 14.1 years old), the 12 ADHD (11 $\pm$ 14.8 years old) patients exhibited significant resting-state brain activities in the bilateral VI/VII (BA 17/18/19), left SI (BA 3), left AII (BA 22), bilateral thalamus, left dorsal brainstem and midbrain [19]. For 29 boys with ADHD (11.00 $\pm$ 16.50 years old) and 27 matched controls (11.25 $\pm$ 14.92 years old), Cao et al. [20] indicated that ReHo of ADHD patients decreased in the frontal–striatal–cerebellar circuits, but increased in the occipital cortex. However, study of ADHD with small sample size is difficult to cover the brain activity patterns of ADHD which vary with age.

In this study, a large rs-fMRI dataset with 266 ADHD subjects and 719 TD subjects from 7 to 16 years old were adopted. ALFF, fALFF and ReHo of each subject were calculated and compared to study the abnormal brain activity of ADHD.

2 Method

2.1 Dataset

Data were acquired from the database–1000 Functional Connectomes Project (1000-FCP) [21]. It is a neuroimaging database that collects resting-state fMRI data from multiple sites. For the TD participants in our study, inclusion criteria included: age from 7 to 16 years old, with no mental disease, image at least cover 95% of brain. Especially, the ADHD data are acquired from the ADHD-200 dataset, which is a sub set of 1000-FCP. It contains resting-state fMRI and anatomical MRI images aggregated

across 8 independent imaging sites, which are obtained from children and adolescents with ADHD (ages: 7–21 years old). Finally we got 266 ADHD subjects and 719 TD subjects with age from 7 to 16 years. To further explore the developmental changes of regional brain activities in ADHD, We divided the TD participants and the ADHD participants into two groups respectively, one for childhood from 7 to 11 years old (TD: 407; ADHD: 169) and the other for adolescence from 12 to 16 years of old (TD: 312; ADHD: 97).

2.2 Image Processing

Resting state fMRI data were preprocessed with DPARSF [22]. The first ten time point was removed to avoid magnetization instability. All images were corrected for slice timing to minimize the difference during image acquisition and realigned to the middle volume to avoid excessive head motion. Then, these images were spatially normalized to a standard template (Montreal Neurological Institute) and resampled to 3 mm × 3 mm × 3 mm voxel resolution. Spatial smoothing was performed with a Gaussian kernel of 4 mm full-width at half-maximum (FWHM) to improve the SNR (signal-to-noise ratio). Besides, the mean signal of white matter and cerebrospinal fluid were removed as covariates. After that, linear trend removal as well as band-pass filtering (0.01–0.1 Hz) were also performed. The brain is divided into 90 ROIs by AAL (automated anatomical labeling) atlas [23] in order to further localize the local variation. Finally, ALFF, fALFF and ReHo of each voxel across participants were be calculated with REST [24].

3 Statistics Analysis

All statistics analysis were performed with SPM12 [25].The brain activity measurements (ALFF, fALFF and ReHo) between ADHD and TD are compared by two-sample t-test on each voxel, taking a significant threshold of $P < 0.01$, with age as covariate, and corrected for multiple comparisons with false discovery rates (FDR). Voxels with $P < 0.01$ and cluster size > 270 mm^3 were regarded to show a significant group difference. We also performed two-sample t-test on ALFF, fALFF and ReHo for childhood and adolescence groups with the method above.

4 Result

4.1 The Comparison of ALFF, fALFF and ReHo Between Two Groups

Compared with TD, ADHD showed significant divergence of ALFF, fALFF and ReHo in extensive regions. The main group differences between ADHD and TD on three measures are shown on Table 1 and Fig. 1.

4.2 The Comparison of ALFF, fALFF and ReHo of Two Age Groups

As we can see, there were some subtle but important differences of the three measurements between two groups in childhood and adolescence. The main age groups differences between ADHD and TD on three measures are shown on Table 2 and Fig. 2.

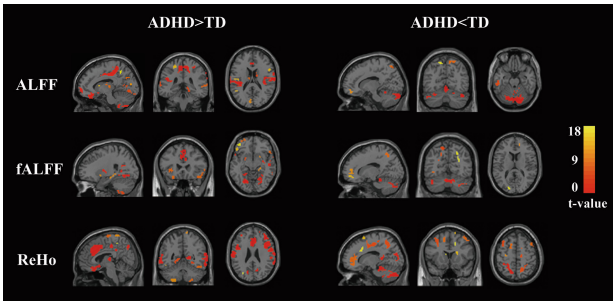

Fig. 1. The bright areas mean that the major differences between all ADHD subjects and all TD subjects. (ADHD: Attention deficit hyperactivity disorder group, TD: Typically developing group)

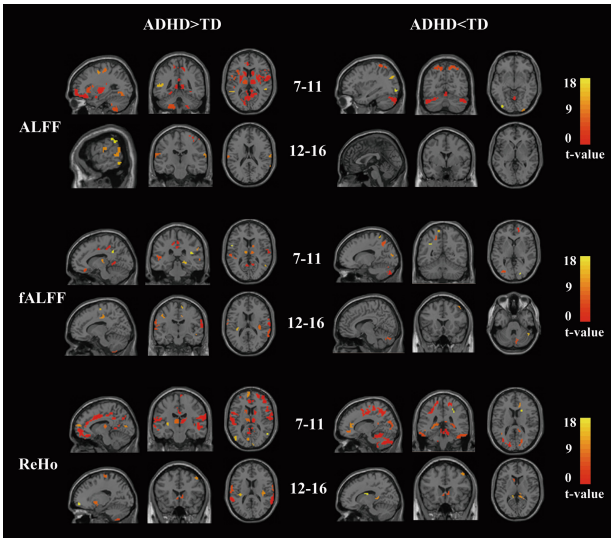

Fig. 2. The bright areas mean that the major differences between ADHD and TD in different age groups. (ADHD: Attention deficit hyperactivity disorder group, TD: Typically developing group)

Table 1. Regions showing significant differences in ALFF, fALFF and ReHo between the ADHD and TD

Regions	p-value	Regions	p-value
ALFF: ADHD > TD		**ALFF: ADHD < TD**	
Left caudate nucleus	0.01	Right superior occipital lobe	<0.01
Left medial superior frontal cortex	0.002	Left superior temporal gyrus	<0.001
Bilateral postcentral gyrus	0.002	Bilateral precuneus	<0.001
Right pallidum	<0.001	Bilateral cerebellum	0.001
Bilateral thalamus	0.004		
Bilateral putamen	0.004		
Vermis	0.001		
fALFF: ADHD > TD		**fALFF: ADHD < TD**	
Bilateral superior frontal cortex	<0.001	Right anterior cingulate cortex	0.002
Right supplementary motor area	0.014	Bilateral superior parietal lobe	0.001
Bilateral pallidum	0.009	Bilateral superior occipital lobe	0.002
Bilateral putamen	0.001	Right precuneus	0.007
Bilateral thalamus	<0.001	Bilateral cerebellum	0.001
Right caudate nucleus	0.011		
Vermis	0.001		
ReHo: ADHD > TD		**ReHo: ADHD < TD**	
Bilateral cerebellum	0.002	Right anterior cingulate cortex	<0.001
Bilateral precentral gyrus	0.02	Bilateral inferior occipital lobe	<0.001
Bilateral supplementary motor area	<0.001	Bilateral superior frontal cortex	0.002
Right postcentral gyrus	<0.001	Bilateral cerebellum	0.003
Left thalamus	0.001		
Right caudate nucleus	0.001		
Right inferior parietal lobe	0.002		

Table 2. Regions showing significant differences in ALFF, fALFF and ReHo between the ADHD and TD in two age groups

Regions	p-value	Regions	p-value
ALFF: ADHD > TD (childhood)		**ALFF: ADHD < TD (childhood)**	
Left insula	<0.001	Bilateral superior parietal lobe	0.004
Right superior frontal cortex	0.001	Bilateral inferior occipital lobe	0.001
Bilateral precentral gyrus	<0.001	Bilateral cerebellum	0.001
Left thalamus	<0.001		
Left precuneus	<0.001		
Left anterior cingulate cortex	<0.001		
ALFF: ADHD > TD (adolescence)		**ALFF: ADHD < TD (adolescence)**	
Right postcentral gyrus	0.001	left angular gyrus	0.002
Right caudate nucleus	0.001	Right medial superior frontal cortex	0.001
Left cerebellum	0.005	Left occipital lobe	0.001
Right inferior frontal cortex	0.001	Bilateral cerebellum	<0.001
fALFF: ADHD > TD (childhood)		**fALFF: ADHD < TD (childhood)**	
Bilateral precuneus	0.005	Right anterior cingulate cortex	0.002
Left supplementary motor area	0.007	Bilateral superior parietal lobe	0.001

(*continued*)

Table 2. (*continued*)

Regions	p-value	Regions	p-value
Right paracentral lobule	0.002	Bilateral superior occipital lobe	0.002
Right postcentral gyrus	0.013	Right precuneus	0.007
Bilateral thalamus	0.006	right cerebellum	0.005
Left medial superior frontal cortex	0.002		
fALFF: ADHD > TD (adolescence)		**fALFF: ADHD < TD (adolescence)**	
Bilateral postcentral gyrus	0.002	Right cerebellum	<0.001
Right supplementary motor area	0.007	Right middle frontal cortex	0.013
Right middle cingulate cortex	0.005		
Left insula	0.008		
Left middle orbital frontal cortex	0.004		
ReHo: ADHD > TD (childhood)		**ReHo: ADHD < TD (childhood)**	
Left putamen	0.008	bilateral superior parietal lobe	<0.001
Left superior medial frontal cortex	0.008	Left inferior occipital lobe	0.003
Left caudate nucleus	<0.001	Right superior frontal cortex	<0.001
Right postcentral gyrus	<0.001	Bilateral cerebellum	<0.001
left anterior cingulate cortex	<0.001		
ReHo: ADHD > TD (adolescence)		**ReHo: ADHD < TD (adolescence)**	
Bilateral pallidum	<0.001	Right precuneus	0.009
Right superior frontal cortex	0.006	Right posterior cingulate cortex	0.002
Left putamen	<0.001	Left thalamus	0.009
Left paracentral lobule	<0.001	Right middle frontal cortex	0.003
Bilateral insula	<0.001		
Right supplementary motor area	<0.001		
Verimis	0.001		

5 Discussion

In this study, three measurements were used to describe the voxel-based local changes in brain activities from different aspects. Firstly, ALFF reflects the level of spontaneous activity of single voxel according to the level of oxygen content, which can directly observe the changes of regional brain activities [9]. Similar to ALFF, fALFF is the ALFF of a given frequency band expressed as a fraction of the sum of amplitudes across the entire frequency range in a given signal, which represents the relative contribution of specific low frequency oscillations to the whole detectable frequency range [26]. Finally, ReHo depicts the coherence of neural activity of a specific brain region with its neighboring or adjacent brain regions [27]. Using the three measurements, we found, after removing the confounding factor age, all ADHD subjects showed abnormal regional activities in the movement pathway and cognitive control circuits, which was in line with previous studies [28, 29]. For all of three measurements, on the one hands, ADHD showed stronger activation than TD in the parts of basal ganglia (caudate nucleus, putamen and pallidum), supplementary motor area, precentral gyrus, cerebellum and thalamus which was related to dysfunction of movement control and execution functions [30, 31]. On the other hands, ADHD

exhibited the lower activation than TD in superior occipital lobe in three measurements, which may be associated with attention lapse [32]. Besides, there were its unique activation areas for each index which was mainly concentrated in brain areas involved in advanced cognitive control. For example, the decreased ALFF, fALFF and ReHo appeared in the left superior temporal gyrus, right anterior cingulate cortex and superior frontal cortex respectively.

From the developmental point of view, compared to TD group, the ALFF of left anterior cingulate cortex (ACC) in ADHD group was significantly increased in childhood, which may be connected to compensation mechanism of inattention in ADHD [10]. But in adolescence, there was no significant difference. The result may demonstrate that the degree of ADHD symptoms has improved with age, which could be associated with drug treatment and other factors [33]. As for fALFF, the difference between the two age groups was not very obvious, which was caused by the insensitivity of fALFF to age. Finally, in childhood, the ReHo value of ACC in ADHD was higher than TD, but the differences of ReHo between ADHD and TD disappeared in adolescence. This result suggests that the complex cognitive ability of patients with ADHD has improved with age, specially, in the aspects of regulating stimulus selection and response selection in the attention process [13]. In contrast, the decreased ReHo of ADHD appeared at left inferior occipital lobe in childhood and disappears in adolescence, which could be related to pay attention to multiple irrelevant visual stimuli from the environment simultaneously. Thus, the abnormal activities of ACC and left inferior occipital lobe may jointly result in inattention problems with ADHD [9, 34].

In conclusion, our study shows the abnormal brain activities of ADHD in rs-fMRI which are different from TD using three measurements (ALFF, fALFF and ReHo) from the perspective of development. Moreover, it facilitates our understanding for the mechanism of ADHD and examines the effectiveness of these three measurements. However, there are some limitations in this study. First, the gender factor is not considered, which may affect the result. Second, the division standard of age groups is arbitrary to a certain extent and we still need to explore more suitable criterion. Finally, the source of data is acquired from different institutes, which causes some bias of parameter setting that may influence the further analysis.

Acknowledgements. This paper was supported by NFSC (National Natural Science Foundation of China) (Grant No. 61403148).

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