Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study

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In this study, a newly reported regional homogeneity approach was used to analyze blood oxygen level-dependent functional magnetic resonance imaging data on resting state in boys with attention deficit hyperactivity disorder. Boys with attention deficit hyperactivity disorder showed decreased regional homogeneity in the frontal–striatal–cerebellar circuits, but increased regional homogeneity mainly in the occipital cortex. Our findings are consistent with the hypothesis of abnormal frontal–striatal–cerebellar circuits in attention deficit hyperactivity disorder. The regional homogeneity approach may be a potentially useful method in exploring the pathophysiology of attention deficit hyperactivity disorder. *NeuroReport* 17:1033–1036 © 2006 Lippincott Williams & Wilkins.

Keywords: attention deficit hyperactivity disorder, functional magnetic resonance imaging, regional homogeneity, resting state

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder characterized by difficulties with attention, motor overactivity and impulsivity that interfere with normal functioning in various settings [1]. Although the pathophysiology of this disorder remains unclear, some researchers generally presume that the neural basis of this disorder resides mainly in anatomical and functional disturbances of frontal–striatal–cerebellar circuits [2].

Volumetric magnetic resonance imaging (MRI) studies have shown abnormalities of the whole brain, the frontal lobes, the basal ganglia, the parietal lobes, the occipital lobe, the cerebellum and so on [3–5]. Several positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies have reported atypical brain activity in hyperactivity disorder in the resting state [6–9]; these abnormal regions include the prefrontal cortex, striatum, occipital cortex and cerebellum. Recently, task-specific blood oxygen level-dependent (BOLD) functional MRI (fMRI) studies have been performed to explore the pathophysiology of ADHD, but the results were inconsistent. For example, hypofrontality in ADHD was found in one study [10], but another study indicated hyperfrontality [11]. Such discrepancy could be due to different tasks, ages and comorbidity in these studies. Moreover, different baseline-activity level may also contribute to the inconsistency among task-specific fMRI studies.

In the first resting-state fMRI study, Biswal and colleagues [12] found that low-frequency fluctuation was highly synchronous among motor cortices. The authors concluded that low-frequency fluctuation of blood flow and oxygenation was indeed a neurophysiological index. Since then, resting-state fMRI is being more and more widely researched. Most of these studies, however, have used functional connectivity analysis: measuring the correlation coefficients of all brain areas with a predefined region of interest. An area showing abnormal functional connectivity with other areas may not be necessarily abnormal itself. Therefore, it is important to investigate the regional activity.

A newly developed fMRI approach on the basis of regional homogeneity (ReHo) measures the similarity of time series of a given voxel to those of its neighbors. Therefore, ReHo reflects the temporal synchrony of the regional BOLD signal. This method has been used to explore regional neural activity pattern in healthy volunteers and psychiatric patients in the resting state [13–16]. Previous studies [13,14] indicated that, during the resting state, the higher ReHo pattern found with fMRI in normal subjects was highly consistent with the pattern of higher metabolism found with PET. A recent study reported that decreased ReHo was found in many brain areas in schizophrenia patients by using resting-state fMRI, these decreased ReHo regions being considered to be involved in the psychopathology and pathophysiology of schizophrenia [16]. This study suggested that the ReHo approach could be potentially useful in revealing the pathophysiology of psychiatric disorders in the resting state.

Using resting-state fMRI and ReHo method, the current study was aimed at exploring the regional brain activity of boys with ADHD.

Methods

Participants

Participants comprised 29 boys with ADHD (11.00–16.50 years, 13.34 ± 1.44 years) and 27 age-matched and sex-matched controls (11.25–14.92 years, 13.08 ± 0.93 years). Six patients and six controls were excluded from further analysis because of excessive head motion (see Data analysis), hence there were 23 ADHD boys (11.00–16.5 years, 13.37 ± 1.49 years) and 21 controls (11.25–14.92 years, 13.32 ± 0.95 years) left. All participants met the following criteria: (1) right-handedness, (2) no lifetime history of head trauma with loss of consciousness, (3) no history of neurological illness or other serious psychical disease, (4) full scores on the Wechsler Intelligence Scale for Chinese Children–Revised higher than 80 [17]. The patients were recruited from the outpatients at Peking University Institute of Mental Health. A structured diagnostic interview, the Clinical Diagnostic Interviewing Scale [18], which is based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, was administered to diagnose ADHD. The inclusion criteria for ADHD were: (1) predominantly inattention type (ADHD-I) or combined type (ADHD-C), (2) no history of emotional disorders, affective disorders, Tourette disorder and other Axis I psychiatric disorder, (3) no evidence of severe language development delay and communication problems as determined through clinical history, parents interview and observation of the children. Boys with hyperactivity disorder with comorbid conduct disorder or oppositional defiant disorder were not excluded. Fifteen patients met criteria for ADHD-I and eight for ADHD-C. Nineteen of 23 patients were stimulants naïve and the other four patients were withheld from stimulants at least 48 h before the MRI scanning. Four had comorbid oppositional defiant disorder and two had comorbid conduct disorder. Controls were recruited from local middle school. They were excluded from the diagnosis of ADHD according to Clinical Diagnostic Interviewing Scale and had no history of emotional disorders, affective disorder, Tourette disorder and other Axis I psychiatric disorder. This study was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University. After complete description of the study procedures, written informed consent was obtained from parents or guardians of all participants. All children agreed to participate.

The definition of resting state

Resting state was defined as no specific cognitive task during the fMRI scan. Participants were required simply to keep still as much as possible, close their eyes and not to think of anything systematically [12,13,16].

Magnetic resonance imaging scanning

MRI data were acquired using a Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany) in the Institute of Biophysics, Chinese Academy of Sciences. Participants lay supine with head snugly fixed by belt and foam pads to minimize head movement. The resting-state functional images were acquired by using an echo-planar imaging sequence with the following parameters: 30 axial slices, thickness/skip=4.5/0 mm, in-plane resolution=64 × 64, repetition time =2000 ms, echo time=30 ms, flip angle=90°, field of view=220 × 220 mm, 240 volumes (8 min). In addition, a T_1-weighted sagittal three-dimensional spoiled gradient-recalled sequence was acquired covering the whole brain (176 slices, repetition time=1700 ms, echo time TE=3.93 ms, slice thickness=1.0 mm, skip=0 mm, flip angle=15°, inversion time-1100 ms, field of view=240 × 240 mm, in-plane resolution=256 × 256). Part of these fMRI data (11 ADHD and nine controls) were used by Zhu *et al.* [15] in a discriminative analysis study to differentiate ADHD from controls, in which ReHo maps were used as an index of resting-state brain function for classification. Seven ADHD and eight control data from the study of Zhu *et al.* were used to investigate the functional connectivity pattern difference between two groups in another study [19].

Data analysis

The first 10 volumes of each functional time series were discarded for participant adaptation to the scanning. Parts of image preprocessing, including slice timing, head motion correction and spatial normalization, were conducted by using statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm). After the procedure of head motion correction, the values for translation (mm) and rotation (degrees) were obtained at each time point in six parameters (three for translation and three for rotation) for each participant. Participants (six from ADHD group and six from control group) with head motion more than 2.0 mm maximum displacement in any direction of x, y, and z or 1.0° of any angular motion throughout the course of scan were excluded from further analysis. Software of Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) was then used for the remaining analysis except for ReHo analysis. The fMRI data were temporally band-pass filtered ($0.01 < f < 0.08$ Hz) to reduce the low-frequency drift and physiological high-frequency respiratory and cardiac noise. Linear trend was then removed.

Individual ReHo map was generated by calculating Kendall's coefficient concordance (with value from 0 to 1) [20] of time series of a given voxel with those of its nearest neighbors (26 voxels) in a voxel-wise way. This procedure was performed with in-house software ReHofMRI11.0 (http://www.nlpr.ia.ac.cn/english/mic/YongHe/Research.htm). ReHo maps were transformed to Talairach and Tournoux coordinates [21]. Spatial smoothing was conducted on the ReHo maps with a Gaussian kernel of $4 \times 4 \times 4\,\mathrm{mm}^3$ full-width at half-maximum. The intracranial voxels were extracted to make a mask [22]. For standardization purposes, each individual ReHo map was divided by its own mean ReHo within the mask.

Statistics

Group differences in age, intelligence quotient (IQ) and head motion (translation and rotation) were analyzed by using Student's t-test. Although the total translation and rotation had no difference between the two groups (P=0.509 and 0.069, respectively), the total rotation in the ADHD group had a trend-level significance higher than that in normal controls (P=0.069). For strictly controlling the influence of head motion on ReHo analysis, total rotation and translation were treated as covariance to analyze the ReHo difference between the two groups.

Two-sample t-test was performed on the normalized individual ReHo maps using total rotation and translation as covariance (http://afni.nimh.nih.gov/sscc/gangc/ANCOVA.html). The resultant statistical map was set at a combined threshold of $P<0.005$ and a minimum cluster size of 270 mm^3, which resulted in a corrected threshold of $P<0.05$ determined by AlphaSim in AFNI (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Results

The age between the two groups had no significant difference (ADHD: 13.37±1.49; controls: 13.32±0.95, P=0.892). The head motion difference was not significant between the two groups (total translation: ADHD 183.77±93.43, control 164.17±101.86, P=0.509; total rotation: ADHD 2.92±2.72, control 1.73±1.14, P=0.069). The controls had higher IQ than that in boys with hyperactivity disorder (ADHD: 101.22±10.10; controls: 115.83±11.58, $P<0.001$).

As shown in Table 1 and Fig. 1, the decreased ReHo regions in ADHD included the bilateral inferior frontal gyrus, right anterior cingulate cortex, left caudate, bilateral pyramis and left precuneus. Brain areas with significant increased ReHo were located in the bilateral lingual gyrus and bilateral cuneus, right culmen and left parahippocampal gyrus.

Discussion

Although the pathophysiology underlying ADHD is unclear, there is a growing notion that the pathophysiology of this disorder may involve frontal–striatal–cerebellar circuits [2]. In the current study, using resting-state fMRI and ReHo method, we found decreased ReHo regions in the frontal–striatal–cerebellar circuits in boys with ADHD.

The prefrontal cortex had been assumed the main disturbed brain regions in ADHD. Several results from structural and functional MRI studies have proved this hypothesis [3–5]. Using automated computational image analysis, Sowell *et al.* [23]reported reduced brain surface extent in inferior portions of the prefrontal cortex. Resting-state SPECT study also found decreased regional cerebral blood flow (rCBF) in the orbitofrontal cortex in ADHD [9]. Human cortical lesion study found that the inferior frontal gyrus was critical for response inhibition [24], the function of which was hypothesized as the core deficit in ADHD [25]. In the current study, we used resting-state fMRI and found decreased inferior frontal gyrus function in boys with ADHD. This result is consistent with the hypofrontality hypotheses of ADHD.

A growing body of neuroimaging evidence supports a role for abnormality of the caudate in ADHD. Anatomical research found that ADHD had smaller caudate volume. The asymmetry of caudate in ADHD was also different from that of normals [3,4]. In the resting state, the caudate was hypoperfused [6] and methylphenidate could increase the perfusion of this region in SPECT studies [7,9]. Our finding of decreased ReHo in the left caudate nucleus in the resting state provided additional evidence for abnormality of the caudate in ADHD.

The cerebellum has been recently recognized as having an important role in the pathophysiology of ADHD. Structural

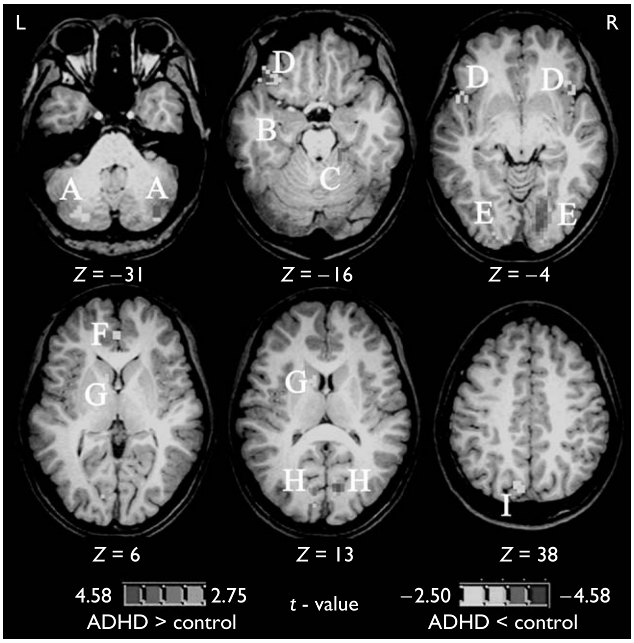

Fig. 1 Brain areas showing regional homogeneity difference between two groups. A, pyramis; B, parahippocampal gyrus; C, culmen; D, inferior frontal gyrus; E, lingual gyrus; F, anterior cingulate; G, caudate; H, cuneus; I, precuneus.

Table 1 Brain areas of ReHo difference between two groups

Areas	Hemisphere	BA	Talairach coordinates (x, y, z)	Volume	Peak t-value
Decreased ReHo in ADHD					
Inferior frontal gyrus	R/L	47/47	38, 23, −4/−38, 26, −16	405/972	3.98/4.45
Anterior cingulate	R	32	2, 44, 3	540	3.23
Caudate	L		−8, 8, 12	324	3.53
Pyramis	R/L		32, −74, −31/−29, −77, −31	3564/351	4.11/3.44
Precuneus	L	7	−8, −71, 39	270	3.46
Increased ReHo in ADHD					
Lingual gyrus	R/L	18/17	14, −83, −4/−11, −92, −7	3105/783	4.58/3.96
Cuneus	R/L	18/18	11, −74, 15/−8, −77, 18	864/972	4.27/4.01
	L	17	−23, −92, −1	783	3.32
Culmen	R		20, −29, −16	675	3.94
Parahippocampal gyrus	L	38	−32, 2, −10	324	3.21

R, right; L, left; BA, Brodmann area; ReHO, regional homogeneity; ADHD, attention deficit hyperactivity disorder.

MRI studies have shown that cerebellum volume was smaller in ADHD, especially in the posterior inferior lobules [3,5]. In a recently reported SPECT study of ADHD in children, Lee *et al*. [9] found decreased rCBF in the bilateral cerebellum relative to control subjects in the resting state. A PET study showed that methylphenidate could increase rCBF in the posterior cerebellum in the resting state for ADHD [8]. The current study found decreased ReHo in ADHD relative to controls in the bilateral cerebellum. All the above findings indicate cerebellar hypofunction in ADHD.

In the current study, the occipital cortex was found to be associated with higher ReHo in hyperactivity disorder. Several SPECT studies performed in the resting state have demonstrated that the occipital cortex was relatively hyperperfused in ADHD and that methylphenidate tended to decrease flow to this area [6,7,9]. The abnormality of these regions may be due to 'a lack of inhibition of sensory perception' and suggested that 'lack of striatal inhibition of polysensory activity is a part of the pathogenetic mechanism in ADHD' [7].

In our study sample, the boys with ADHD had lower IQ than that of controls (ADHD: 101.22 ± 10.10; controls: 115.83 ± 11.58, $P < 0.001$). Correlative analysis was conducted between IQ and ReHo value in two voxels (located in the left inferior frontal gyrus and right lingual gyrus, peak t-value$=-4.445$ and 4.5803, respectively, which showed the most significant difference between two groups) in controls and ADHD groups respectively. As no significant correlation was found between these two variables in two groups ($|r| < 0.285$, $P > 0.187$) and there were no studies indicating that IQ affected the value of ReHo, IQ was not treated as a covariance in image data analysis. More work will, however, be needed to understand the relationship between IQ and ReHo. In addition, the relationship between the value of ReHo and the volume of the corresponding brain structure needs to be investigated in the future study, that will help understand the mechanism of ReHo.

Conclusion

In the current study, using the regional homogeneity approach to analyze BOLD–fMRI data in the resting state, we found that boys with ADHD showed decreased ReHo areas included in the prefrontal–striatal–cerebellar circuits, which provided additional evidence for the hypothesis that frontal–striatal–cerebellar circuits were involved in the pathophysiology of ADHD. Our results were consistent with the findings in previous studies. The results indicated that, relative to normal controls, boys with ADHD have an atypical pattern of brain activity in the resting state and the ReHo may be a useful approach in understanding the pathophysiology of ADHD.

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