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Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder

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Abstract

Dorsal anterior cingulate cortex (dACC) has been found to function abnormally in attention deficit hyperactivity disorder (ADHD) patients in several former functional MRI (fMRI) studies. Resting-state low-frequency fluctuations (LFFs) of blood oxygen level-dependent (BOLD) fMRI signals have been proved to be quite informative. This study used resting-state LFFs to investigate the resting-state functional connectivity pattern differences of dACC in adolescents with and without ADHD. As compared to the controls, the ADHD patients exhibited more significant resting-state functional connectivities with the dACC in bilateral dACC, bilateral thalamus, bilateral cerebellum, bilateral insula and bilateral brainstem (pons). No brain region in the controls was found to exhibit more significant resting-state functional connectivity with the dACC. We suggest these abnormally more significant functional connectivities in the ADHD patients may indicate the abnormality of autonomic control functions in them.

Keywords: Attention deficit hyperactivity disorder (ADHD); Functional magnetic resonance imaging (fMRI); Resting-state; Functional connectivity; Autonomic control

Attention deficient hyperactivity disorder (ADHD) is characterized by age-inappropriate symptoms of inattention, hyperactivity, and impulsivity. It arises in childhood and often persists into adolescence, or even into adulthood. Many functional neuroimaging studies have been carried out to discover the pathologies underlying the disorder. Convergent evidence has implicated fronto-striatal network abnormalities as the core deficits of ADHD [7,33,36].

Blood oxygenation level-dependent (BOLD) fMRI is a valuable technique for ADHD pathology analysis [5,14,30,32]. Up to the present time, all former BOLD fMRI studies on ADHD are task-based, that is, they analysed ADHD pathologies by evaluating the brain activity pattern differences between the ADHD patients and their matched controls in certain cognitive tasks. As compared to task-based fMRI studies, studies carried out during resting-state are easy to carry out (without experiment designing and subject training) and comparable across different patient groups. Moreover, a study carried out during resting-state would provide us a new perspective on ADHD pathology. In fact, using a procedure named "T2 relaxometry" that indirectly assesses blood volume, two resting-state fMRI studies have been carried out on ADHD pathology analysis [1,37].

Functional connectivity describes spatiotemporal correlations between spatially distinct brain regions [16]. Using this concept, correlations between low frequency fluctuations (LFFs) of resting-state BOLD signals have been found in motor, auditory, visual and language systems [3,8,18,24]. Recently, resting-state LFFs have been applied to the pathology analyses of such neuropsychiatric disorders as Alzheimer's disease [23] and multiple sclerosis [25]. To the best of our knowledge, prior to this study there have not been any resting-state LFFs studies on ADHD.

The anterior cingulate cortex (ACC), especially its dorsal part (dACC, cytoarchitecture areas 24a′/24b′/24c′/32′ [6]), is an important component of the fronto-striatal circuitry and has been found to function abnormally in ADHD patients in many task-based fMRI studies [5,14,30,32]. It has been suggested to play important roles in both cognitive control [4,28] and autonomic

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control [9,12], and both of these two functions have been found to be abnormal in ADHD patients [5,14,21,27,30,32]. Accordingly, focusing on dACC may be beneficial for ADHD pathology analysis.

The goal of the present study was to compare the resting-state dACC functional connectivity patterns in adolescents with and without ADHD. We hypothesize that either the functional connectivities between dACC and cognitive control related brain regions, or those between dACC and autonomic control related brain regions, or both kinds of these connectivities, would be abnormal in ADHD patients.

Twelve ADHD patients and 12 controls participated in the study. Inclusion criteria for all subjects were: within the age range of 11–15 years, male, right-handedness, and IQ > 80 (as assessed with Wechsler Intelligence Scale for Children-revised (WISC-R)). Exclusion criteria for all subjects were: any contraindications for MRI and any neuropsychiatric disorder (including childhood schizophrenia, depression, anxiety, mental retardation and epilepsy). Group matching was based on age, gender, and education. We chose adolescents, rather than children, in this study in order to reduce the possibility of movement artifacts [30].

All the 12 ADHD patients (range 11–14.8 years, mean 13.48 ± 1.11 years) met the DSM-IV criteria for ADHD (as assessed with Clinical Diagnostic Interview Scale, CDIS). Ten of them were of the inattention subtype, and the other two were of the combined subtype. Eleven of the ADHD patients were medication-free for at least half a year, and one was taken off medication for only 48 h. All the 12 ADHD adolescents were outpatients of the Institute of Mental Health, Peking University. The controls (range 12.5–14.1 years, mean 13.19 ± 0.49 years) were enrolled from the nearest middle school. All the 24 subjects were of the Han race.

Due to excessive head motions, functional images of eight ADHD patients (13.91 ± 0.35 years, seven of inattention subtype and one of combined subtype) and 10 controls (13.20 ± 0.56 years) were available for further analysis. To facilitate sample-size matching, the two youngest of the 10 available controls were further excluded from statistical analyses (eight controls, 13.36 ± 0.50 years).

The parents of all participants gave written informed consents after receiving a complete description of the study. This study was approved by the Research Ethics Review Board of Institute of Mental Health, Peking University and that of Institute of Biophysics, Chinese Academy of Sciences.

The imaging studies were done using a SIEMENS TRIO 3-Tesla scanner at the Beijing MRI Center for Brain Research. During the resting-state, subjects were told not to concentrate on any particular subject, but just to relax with their eyes closed. Echo Planer Imaging (EPI) BOLD images were acquired axially using the following parameters: 2000/30 ms (TR/TE), 30 slices, 4.5/0 mm (thickness/gap), 220 mm × 220 mm (FOV), 64 × 64 (resolution), 90° (flip angle). Each session lasted for 480 s. The high-resolution T1-weighted spoiled gradient-recalled whole-brain volume was acquired sagittally using the following parameters: 1700/3.92 ms (TR/TE), 176 slices, 1.0/0 mm (thickness/gap), 256 mm × 256 mm (FOV), 256 × 256 (resolution), 12° (flip angle). Other series, which have no relation to the present study, are not described here.

The functional scans were first corrected for within-scan acquisition time differences between slices and realigned to the first volume to correct for inter-scan movements. The functional scans were then spatially normalized to a standard template (Montreal Neurological Institute) and resampled to 3 mm × 3 mm × 3 mm. Subsequently, the functional scans were spatially smoothed with a 4 mm × 4 mm × 4 mm full width at half maximum Gaussian kernel to decrease spatial noise. All these processes were conducted by using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). Finally, to reduce low-frequency drift and high-frequency noise, the waveform of each voxel was passed through a band-pass filter (0.01–0.08 Hz) by using AFNI (http://afni.nimh.nih.gov/).

Correlational analysis is sensitive to head motions, whereas severe head motions were observed in most subjects during the scanning processes in the present study. We tried to minimize the head motion effects by picking out 150 continuous volumes with relatively less head motions for further analyses. Specifically, among the 91 possible choices, we chose the one that contains the minimum of the maximum of x, y, or z displacements. The datasets with the maximum displacement in either cardinal direction (x, y, z) greater than 1 mm even within these 150 volumes were discarded. As mentioned above, images of four ADHD patients and two controls were excluded from further analyses due to excessive head motions.

Subject specific ROIs were outlined manually on the normalized high-resolution T1-weighted images of each subject by a certificated neuroanatomical specialist. dACC borderlines were determined according to anatomical references ([6], corresponding to the cognitive division of ACC in the paper). The outlined ROIs were then resampled to 3 mm × 3 mm × 3 mm for further analysis.

A seed reference time course was obtained by averaging the time series of all voxels in the subject specific ROI. Pearson's correlation analysis was then performed between the seed reference time course and time series from the whole brain in a voxel-wise way. This produced a spatial map wherein the value of the voxel represented the strength of the correlation with the dACC. Finally, the correlation coefficients were transformed into z-scores using Fisher's transformation to improve normality [29]:

$$Z = \frac{1}{2} \log_e \left(\frac{1+r}{1-r} \right) \quad (1)$$

where r is the correlation coefficient for each voxel.

The resting-state functional connectivity pattern differences between the eight ADHD patients and the eight controls were obtained by a random-effect two-tailed two-sample t-test [20]. The resulting t-map was masked by a grey matter map, which was obtained by segmenting the mean normalized high resolution T1-weighted images of all the subjects, to include only the areas falling in grey matter. A combined threshold and clustering approach was performed to correct for multiple comparisons. The random distribution of cluster sizes for a given per voxel

threshold was determined by Monte Carlo simulations [22]. According to this distribution, a corrected P-value of $P<0.05$ can be achieved through the combination of a per voxel threshold of $P<0.05$ and a cluster size of at least 1188 mm^3. Statistical map were superimposed on the mean normalized high resolution T1-weighted images of all the subjects.

As has been mentioned, correlational analysis is very sensitive to gross head motion effects. To make sure that the two groups had similar head motion characteristics, we further evaluated the between group maximum head motion differences and between group mean head motion differences by two-tailed two-sample t-tests [20]. Here, the maximum head motion was defined as follows:

$$\text{HeadMotion}_{\max} = \max_{x,y,z}(\max(\overline{\Delta x}) - \min(\overline{\Delta x}), \max(\overline{\Delta y}) - \min(\overline{\Delta y}), \quad \max(\overline{\Delta z}) - \min(\overline{\Delta z})) \tag{2}$$

where $\overline{\Delta x}$, $\overline{\Delta y}$ and $\overline{\Delta z}$ are $1 \times T$ vectors describing head motions in three cardinal directions x, y and z, respectively. T is the number of volumes, in the present study, $T=150$. And the mean head motion was defined as follows:

$$\text{HeadMotion}_{\text{mean}} = \frac{\sum_{i=2}^{T}\left(\sqrt{(\Delta x_i)^2 + (\Delta y_i)^2 + (\Delta z_i)^2}\right)}{T-1} \tag{3}$$

where Δx_i, Δy_i and Δz_i are head motions at the ith time point in three cardinal directions x, y and z, respectively. T is the number of volumes.

No significant difference was found between the two groups using either the maximum head motion measurement (0.666 ± 0.169 mm for the ADHD patients and 0.665 ± 0.179 mm for the controls, $t=0.01$, d.f. $=14$, $P=0.99$) or the mean head motion measurement (0.060 ± 0.012 mm for the ADHD patients and 0.053 ± 0.019 mm for the controls, $t=0.80$, d.f. $=14$, $P=0.44$). That is, the ADHD patients and the controls in the present study had similar head motion characteristics.

Bilateral dACC, bilateral thalamus, bilateral cerebellum, bilateral insula and bilateral brainstem (pons) were found to exhibit more significant resting-state functional connectivities with dACC in the ADHD patients than in the controls (Fig. 1, Table 1). No brain region was found to exhibit more significant resting-state functional connectivity with dACC in the controls.

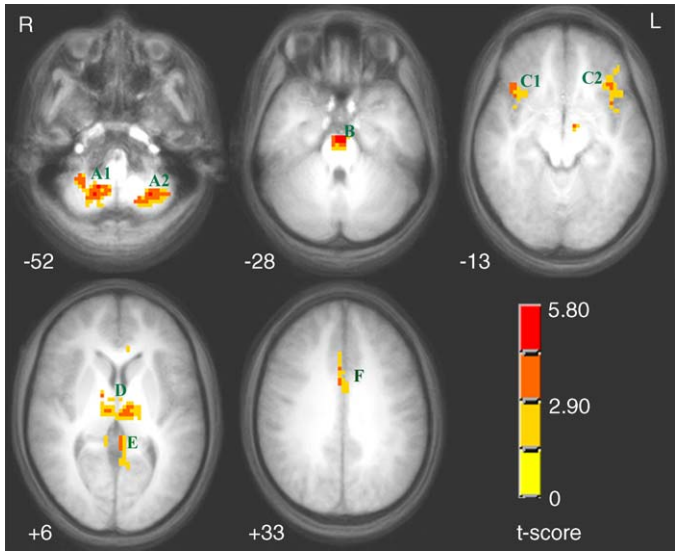

Fig. 1. Map of resting-state dACC functional connectivity pattern differences between the ADHD patients and the controls. T-score scale is shown on the lower right. Bright colour indicates that the ADHD patients have more significant functional connectivities. Threshold was set at $P<0.05$ (corrected). The numbers beneath each image refer to the z coordinates of Talairach. A–F are labels of the approximate locations of clusters exhibited more significant functional connectivities in the ADHD patients. A1 [9, −55, −53], right cerebellum. A2 [−24, −61, −52], left cerebellum. B [3, −19, −27], bilateral brainstem, pons. C1 [36, 14, −16], right insula. C2 [−45, 5, −15], left insula. D [6, −6, 0], bilateral thalamus. E [−3, −38, 7], bilateral PCC. F [3, 8, 36], bilateral dACC. L, left; R, right.

This study, to our knowledge, was the first fMRI study to analyze ADHD pathologies during a conscious resting-state from a network perspective. It was different from the two former resting-state fMRI studies on ADHD [1,37] in three aspects: it used LFFs rather than T2 relaxation time to evaluate brain functions; it analysed ADHD pathologies from a functional integration perspective rather than a functional segregation perspective; and it selected a ROI that was different from those used in the two studies. So the results of the present study are not directly comparable to those of the two studies.

No significant difference was found between the two groups using either the maximum head motion measurement or the

Table 1
dACC functional connectivity pattern differences between the ADHD patients and the controls during conscious resting-state

Area	Volume (mm^3)	Brodman area	Side	Talairach (peak)			t-score (peak)[a]
				x	y	z	
dACC	3699	24/32	Bilateral	3	8	36	4.16
PCC	1566	29/30	Bilateral	−3	−38	7	3.79
Thalamus	3942		Bilateral	6	−6	0	4.39
Insula	3132		Left	−45	5	−15	4.02
Insula	1998		Right	36	14	−16	4.01
Brainstem, pons	2160		Bilateral	3	−19	−27	5.80
Cerebellum	1485		Left	−24	−61	−52	5.07
Cerebellum	4023		Right	9	−55	−53	4.94

The threshold was set at $P<0.05$ (corrected).
[a] t-score >0 signifies the brain region had more significant functional connectivity with dACC in the ADHD patients.

mean head motion measurement. This indicated that the two groups had similar head motion characteristics. Thus the resultant functional connectivity pattern differences between the two groups were less likely to be caused by movement artifacts.

By comparing the resting-state dACC functional connectivity patterns in adolescents with and without ADHD, we found the ADHD patients had more significant functional connectivities with the dACC in such brain regions as bilateral dACC, bilateral brainstem pons, bilateral insula, bilateral cerebellum and bilateral thalamus (Fig. 1, Table 1). The brainstem pons has been found to be particularly involved in homeostatic autonomic regulations [10–12,19,34,38]. The insula has been implicated in representation and control of autonomic information [12,34], especially in representation of body states [13]. The dACC has its crucial role in autonomic control [11–13,19]. The cerebellum has been found to be involved in a number of autonomic functions such as cardiovascular responses representation [19] and conditioned cardiovascular control [17], and has been suggested to act as a functional relay between cortex and brainstem to facilitate cortical modulation of brainstem autonomic nuclei [10]. The thalamus, as a relay centre for sensory information, has also been found to be a critical figure of the autonomic control system [2,19,38]. To sum up, these more significant functional connectivities found in the ADHD patients may suggest the abnormalities of autonomic control functions in them.

Our suggestion of abnormalities of autonomic control functions in the ADHD patients was supported by several other studies on ADHD. Reduced autonomic arousal in ADHD patients has been found in many studies by using such electrodermal indices of arousal as skin conductance level (SCL), skin conductance response (SCR) and the number of non-specific skin conductance responses (NS.SCRs) [21,26,27,31,35]. For instance, Lazzaro et al. found ADHD patients exhibited some autonomic hypoarousal during the resting-state based on their reduced SCL and reduced NS.SCRs [21]; O'Connell et al. found decreased SCRs in ADHD patients in a sustained attention task, and they suggested that the attenuated autonomic responses in ADHD patients might indirectly result in inattention [27].

As has been mentioned, dACC has been suggested to play important roles in both cognitive control [4,28] and autonomic control [9,12]. The dACC abnormalities found in most former fMRI studies on ADHD have been attributed to the abnormalities of its cognitive control functions [5,14,30,32]. However, Fellows and Farah found that dACC was not a necessary component of the cognitive control network [15]. Critchley et al. suggested that the role of dACC in modulation of bodily states of arousal to meet concurrent behavioural demands might account for its activities observed during emotional and executive tasks [12]. If this is the case, then autonomic control deficits in ADHD patients may at least partially account for the dACC functional abnormalities observed in them in former fMRI studies [5,14,30,32].

Further studies can increase the applicability of this research. For example, a simultaneous fMRI and electrodermal activity (EDA) study would give more direct evidence of autonomic control functional abnormalities in ADHD patients; a combination of fMRI and DTI techniques would facilitate a simultaneous investigation of the functional and anatomical connectivity abnormalities in these patients; a study considering subtype effects might benefit discovering the exact etiology and pathologies of specific subtypes; and a larger sample size would increase the generality of our findings.

To summarize, we found dACC had more significant resting-state functional connectivities with several other brain regions in the ADHD patients as compared to the controls. We suggest these abnormally more significant connectivities in ADHD patients may indicate abnormalities of autonomic control functions in them. By virtue of its non-invasiveness, high spatial and temporal resolution, low expense (as compared to PET) and clinical convenience (as compared to task-based studies), resting-state LFFs could be an advantageous choice for ADHD pathology analysis.

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