



Altered patterns of resting-state functional connectivity between the caudate and other brain regions in medication-naïve children with attention deficit hyperactivity disorder

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ABSTRACT

Background: Structural and functional alterations occur in the caudate of patients with attention-deficit/hyperactivity disorder (ADHD). Here we aimed to investigate the functional connectivity between the dorsal caudate and other brain regions in ADHD children.

Methods: Resting-state functional connectivity from 30 ADHD and 33 age- and gender-matched “normal” children were measured by functional Magnetic Resonance Imaging.

Results: Positive connectivity with dorsal caudate was observed in the prefrontal areas, cingulate cortex and temporal lobe. Negative functional connectivity was observed in the precuneus, occipital cortices and cerebellum. The connectivity of left dorsal caudate to left inferior frontal gyrus was correlated with severity of ADHD.

Conclusions: Connectivity of dorsal caudate with several brain regions was identified in ADHD children.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in children especially in school-aged children and it affects about 7% of children based on DSM-IV criteria [1]. It is characterized by alterations of executive functions such as inattention, hyperactivity and/or acting impulsivity, which result in poor school performance [2]. The dorsal caudate (DC) is thought to be primarily involved with the executive function [3,4] and is found to be related with the pathophysiology of ADHD [5]. Previous studies have demonstrated that volume and activity of DC were reduced in ADHD children [6,7]. Due to the integrality of the whole brain, some other brain regions are also involved in executive function such as putamen [8] though they may play different roles. The activity of caudate nucleus is predominantly related to goal-directed cognitive action while the putamen appears to be involved in cognitive functions related to stimulus-response or habitual learning [9]. Moreover, caudate is connected with other brain regions in terms of anatomical and functional connectivity. The head of the caudate is connected to the dorsolateral prefrontal cortex (DLPFC) [10] while DC is found to be coactive with the ventrolateral prefrontal cortex (VLPFC) and anterior cingulate cortex and parietal cortex [3]. It was found that frontal, temporal, and occipital cortices were abnormally connected with the

remainder of the brain in ADHD patients [11]. However, the role of this connection between caudate and other brain regions in ADHD was not clear due to the limitation of evaluation tool.

In the previous studies, some researchers have used resting-state functional magnetic resonance imaging (fMRI) to detect integrative functional connectivity analysis of the striatum in normal subjects [3]. This method has been showed to be correlated with low-frequency (<0.08 Hz) fluctuations of resting-state blood oxygenation level-dependent signals among the motor, auditory, and visual cortices, as well as the language system in normal subjects [12]. In ADHD patients, resting-state fMRI has identified a significantly decreased negative resting-state functional connectivity with the default mode network [13]. Therefore, it may be a potential approach for examining resting-state functional connectivity of the caudate and other brain regions in ADHD children. In the present study, we investigate the alterations of resting-state functional connections between the DC and the brain in children with ADHD. Since medication history might exert complex effects on ADHD-specific neuropathology [14], all ADHD children participating in this study were medication-naïve.

2. Methods

2.1. Patients profile

This study was approved by the Research Ethics Review Board of the Third Affiliated Hospital of Soochow University. Informed consent was

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obtained from the parents of each child who agreed to participate in the study. A total of 32 ADHD children and 36 healthy participants who were age-, gender-, and education-matched were enrolled in the present study. All participants were 7–13 years old, right-handed, and had intelligence quotient (IQ) scores >80 (measured by the Wechsler Intelligence Scale for Chinese Children-Revised). ADHD diagnosis was determined by the Clinical Diagnostic Interviewing Scale [34] based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria using a semi-structured diagnostic interview. The updated revision has not been released in China; therefore, we did not use the DSM-V. In addition, the parents of all participants completed Conners' Parent Rating Scales [15]. The form of ADHD rating scale-IV (ADHD RS-IV) was completed by the parents to address 18 issues corresponding to the DSM-IV criteria for ADHD. Each symptom, if any, was scored according to its severity (i.e., "never" is rated as 1, "occasionally" is 2; "often" is 3; "always" is 4). Two patients with comorbid oppositional defiant disorder and one with conduct disorder were also included. Exclusion criteria were 1) lifetime history of head trauma with loss of consciousness; 2) history of neurological disorders or other severe physical diseases; 3) lifetime history of neuropsychiatric disorders including schizophrenia, affective disorders, anxiety, 4) Tourette's disorder, pervasive developmental disorder and mental retardation as evaluated by the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version [16]); and 5) previous treatment with stimulants.

2.2. Image acquisition

Images were acquired using a SIEMENS 1.5-Tesla MAGNETOM Avanto scanner. During resting-state fMRI scanning, the participants were guided to close their eyes and remain as still as possible in a calm and awake status [17]. Resting-state fMRI data was acquired using an echo-planar imaging (EPI) sequence with the following parameters: 18 axial slices, repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle = 90°, thickness/gap = 6.0/1.2 mm, field of view (FOV) = 240 × 240 mm, matrix = 64 × 64, 180 volumes (6 min). High-resolution T1-weighted 3D images were acquired sagittally, covering the whole brain using the following parameters: TR = 414 ms, TE = 11 ms, flip angle = 90°, in-plane resolution = 256 × 256, FOV = 240 mm × 240 mm and thickness/gap = 5.0/1.5 mm.

2.3. Data analysis

The first ten functional volumes in the acquisition were discarded to avoid any transient signal changes before the magnetization reached a steady-state. The data were then preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSF) V2.0 software package [18]. The data from five participants (two ADHD and three healthy) were excluded from the further analysis due to the head motion exceeding 1 mm of translation or 1° of rotation in any direction. The functional scans were then spatially normalized to a standard template (Montreal Neurological Institute; MNI) and re-sampled to 3 × 3 × 3 mm³. Subsequently, spatial smoothing was conducted using a Gaussian kernel of 4 mm full width at half maximum. Further preprocessing included removal of linear trend and temporal band-pass filtering (0.01–0.08 Hz) was also performed.

Two spherical ROIs (radius = 3.5 mm) were centered at the bilateral DC (MNI coordinates: right DC: x = 13, y = 15, z = 9; left DC: x = -13, y = 15, z = 9) [3]. The averaged time-course was obtained for the bilateral DC-ROIs and taken as the seed time-course for functional connectivity analysis. A total of nine nuisance covariates were regressed out, including global signal, white matter (WM) signal, cerebrospinal fluid (CSF) signal, and six head motion parameters. Therefore, this study focused on the difference between the groups rather than age as covariate in group analyses. Pearson's correlation analysis was performed between the seed reference time-course and the time course of each

voxel in the brain. To enhance normality, the correlation coefficients were transformed into z-scores using Fisher's transformation.

2.4. Statistical analysis

To view the functional connectivity pattern of each DC-ROI, one-sample *t*-test were performed for each side of the DC-ROI functional connectivity z-maps for each group. A corrected threshold of $P < 0.05$ corresponded to a combined threshold of $P < 0.01$ at individual voxel level and cluster size >270 mm³ (10 voxels). The multiple comparison correction was performed using Monte Carlo simulation [19] implemented with REST software, i.e., the AlphaSim program, part of the AFNI software package (<http://afni.nimh.nih.gov>).

Two-tailed two-sample *t*-tests were performed as a measure of the resting-state functional connectivity between the ADHD children and normal controls for the right and left seed DC-ROIs, respectively. Multiple comparison correction for the results of the between-group *t*-test was restricted within two masks, i.e., the right-mask and left-mask as described below. There were two resting-state fMRI one-sample-*t*-maps, one from the ADHD group and another from the normal controls. After thresholding (See above), the two thresholded *t*-maps were merged into one binary right-mask, within which each region exhibited significant functional connectivity with the right DC-ROI in at least one of the two groups. A left-mask was obtained in the same way. For the between-group difference in right DC-ROI functional connectivity, a corrected threshold of $P < 0.05$ corresponded to a combined threshold of $P < 0.01$ at individual voxel level and a minimum cluster size of 405 mm³ (15 voxels). Similarly, for the left DC-ROI, a combined threshold of $P < 0.01$ and a minimum cluster size of 351 mm³ (13 voxels) corresponded to a corrected threshold of $P < 0.05$. Two sample *t*-test results were superimposed on the mask of ch2. In our data analysis, one-sample *t*-tests were tested with a single-tailed way, while two-tailed two-sample *t*-test were performed based on the combined one-sample *t*-maps that, combined two groups of data - one from the normal children and another from the ADHD children. Therefore, our two-tailed two-sample *t*-test was performed in a very strict way.

To investigate the relationship between functional connectivity and symptom severity, Pearson correlation analyses was performed $P < 0.05$ was used as statistical significance.

3. Results

3.1. Demographic data

The demographic and clinical characteristics of the subjects were summarized in Table 1. There were no significant differences of age and IQ between ADHD children and healthy controls. All the children with ADHD showed significantly higher scores on the ADHD RS-IV scale than the healthy controls ($P < 0.05$). The ADHD children showed higher hyperactivity/impulsivity than the control group ($P < 0.05$).

3.2. Functional MRI results

The within-group functional connectivity patterns were analyzed with one-sample *t*-test. Both the left and right DC-ROIs exhibited positive functional connectivity in the bilateral caudate, bilateral superior

Table 1
Summary of the demographic and clinical characteristics of the participants

	ADHD	Controls	<i>P</i> value
Age (y)	10.2 ± 1.1	10.4 ± 1.9	0.610
Full scale IQ	101.3 ± 3.2	104.9 ± 10.1	0.067
ADHD rating scale-IV			
Total score	40.7 ± 6.3	21.6 ± 2.4	<0.05
Inattention	22.8 ± 4.5	11.7 ± 1.8	<0.05
Hyperactivity/impulsivity	17.9 ± 4.2	9.9 ± 2.8	<0.05

temporal gyrus, bilateral middle frontal gyrus, bilateral precentral gyrus and cingulate cortex, right superior/inferior frontal gyrus, right inferior temporal gyrus and left angular gyrus (Fig. 1 A and B). The left and right DC seeds showed a negative correlation with some brain regions such as bilateral precuneus, superior frontal gyrus, right inferior occipital gyrus, right lingual gyrus, left middle occipital gyrus and left parietal lobe. (See Fig. 2.)

For the right DC-ROI, both the left and right inferior frontal gyrus in the ADHD group exhibited positive functional connectivity as compared to the controls. For the left DC-ROI, the positive correlation with left DC-ROI in the ADHD children was increased in left inferior frontal gyrus, left middle frontal gyrus, left superior frontal gyrus and right superior temporal gyrus. In addition, increased negative connectivity was observed in the left cerebellum.

3.3. Correlation between the symptoms and the strength of functional connectivity

We performed a correlation analysis between the connectivity strength (i.e., mean z-values within each cluster) and behavioral assessments in the ADHD group. The strength of functional connectivity of the left DC-ROI to left inferior frontal gyrus exhibited a significant positive correlation with the total ADHD RS-IV scores ($r = 0.754, P < 0.05$) and with inattention subscale scores ($r = 0.864, P < 0.05$).

4. Discussion

In the present study, we found that ADHD children had the positive and negative connectivity of DC with several brain regions and the connectivity of left DC to left inferior frontal gyrus indicated the severity of

ADHD. Our data initially showed positive functional connectivity between the left and right DC-ROIs in the prefrontal areas, cingulate cortex and temporal lobe and negative functional connectivity in the precuneus, occipital cortices and cerebellum. As compared to the normal controls, the left cerebellum in ADHD children exhibited an increased negative connectivity with the left DC-ROI, while an increase in positive functional connectivity with DC-ROIs was observed in the DLPFC, ventrolateral prefrontal cortex and right superior temporal gyrus. Finally, the strength of functional connectivity of the left DC-ROI to left inferior frontal gyrus exhibited a positive correlation with ADHD severity. This result provided novel insight into the underlying mechanism of medication-naïve ADHD.

Grahn et al. [4] have demonstrated that the head of the caudate is linked to prefrontal brain regions in both anatomical and functional connectivity. In the present study, it was found that positive functional connectivity with DC-ROIs was shown in the DLPFC, VLPFC and cingulate cortex of the control group, which strongly demonstrate the existence of relationships between the DC and prefrontal brain regions. Our data was in consistent with previous reports [20,21]. The executive function mainly involves the prefrontal lobe. The DLPFC and VLPFC are thought to process a variety of cognitive functions, including vigilance, selective and divided attention, attention shifting, planning, executive control and working memory [22]. Functional connectivity between the DC and the DLPFC and VLPFC may be involved in executive functioning. The negative correlations may indicate an antagonistic effect [3]. In our study, negative functional connectivity was observed in the precuneus, occipital cortices and cerebellum while Di Martino et al. did not found that in the temporal lobe and cerebellum. This controversy could be due to a difference in the ages of the subjects [3]. We studied the children with an age range from 7 to 13 years while Di Martino

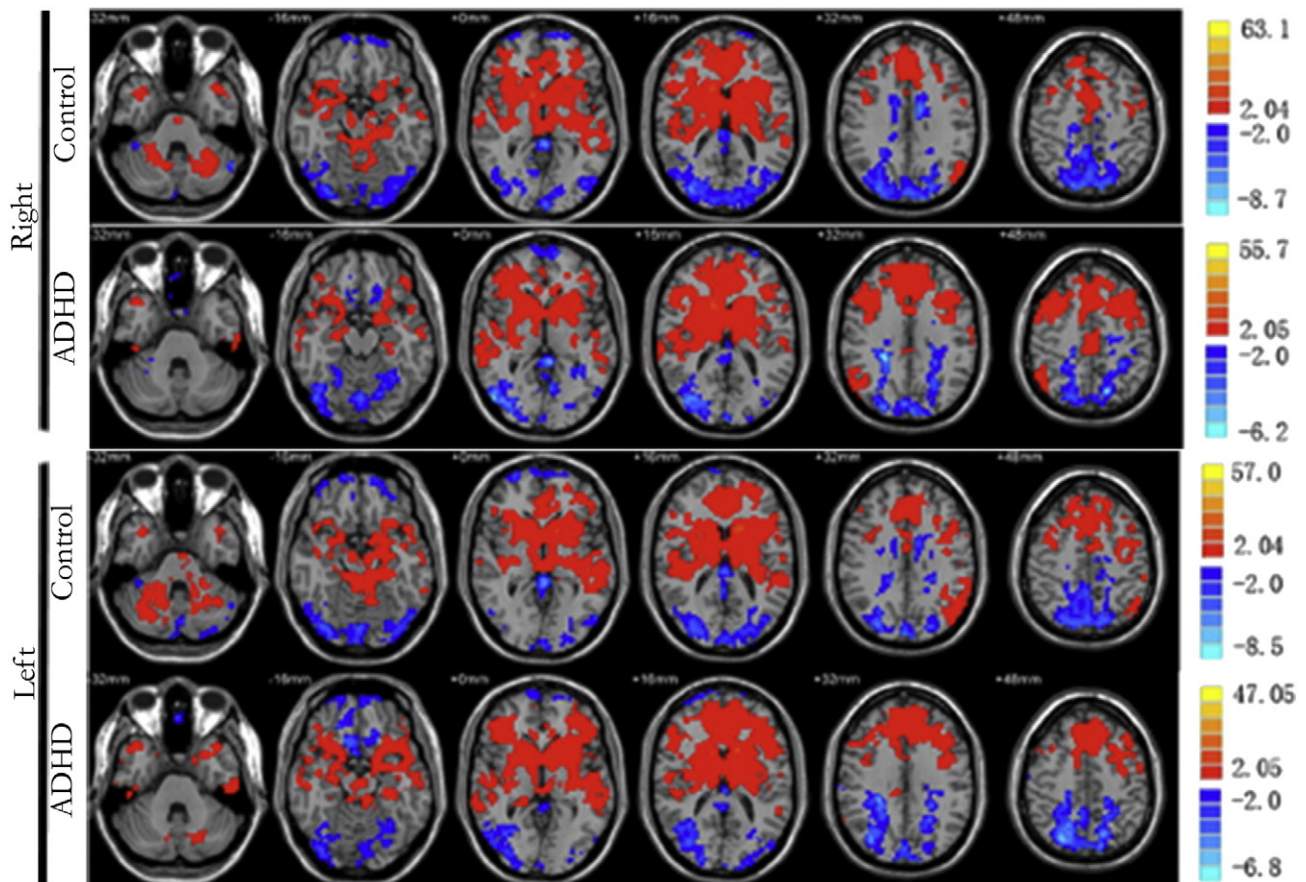


Fig. 1. Functional connectivity of DC with other brain regions. Patterns of significant positive (red) and negative (blue) functional connectivity with the DC-ROIs were observed in the control and ADHD group using fMRI. Threshold was set at $P < 0.05$.

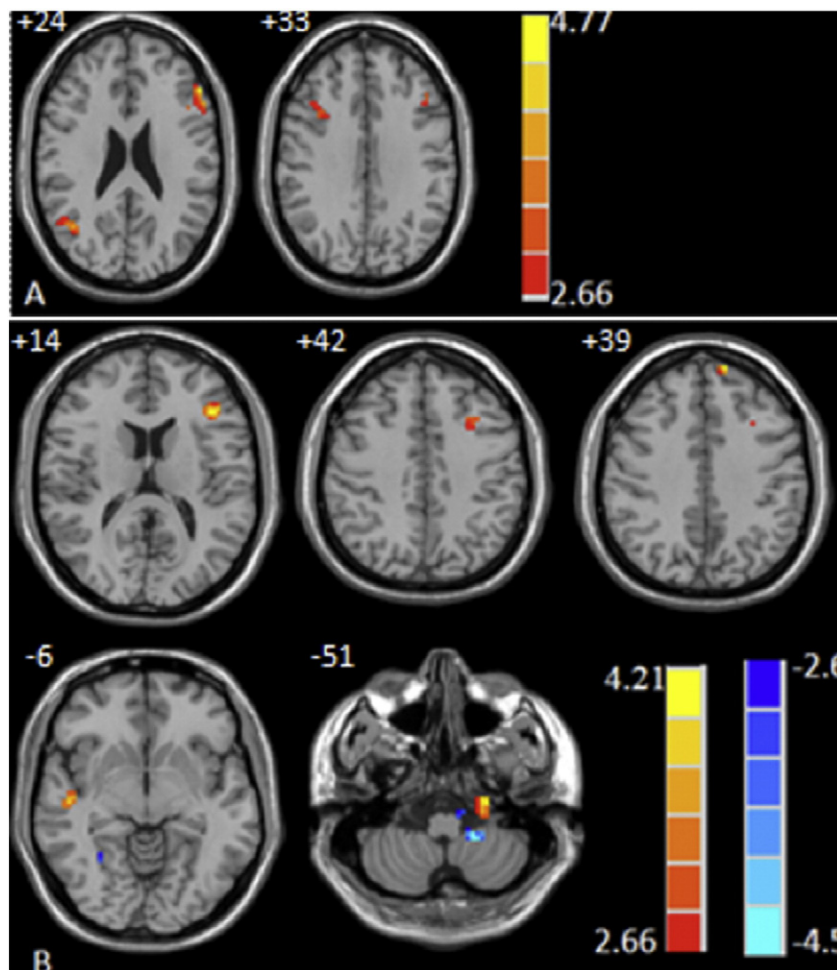


Fig. 2. Altered patterns of functional connectivity between DC and other brain regions (A), There was increased positive functional connectivity of right DC with left (left panel) and right inferior frontal gyrus (right panel) in ADHD patients. (B), the upper row shows regions in ADHD group (from left to right: left inferior frontal gyrus, left middle frontal gyrus, left superior frontal gyrus) exhibiting increased positive functional connectivity when compared to controls in the left DC. The lower row shows changes in different brain regions (from left to right: right superior temporal gyrus, left cerebellum). In the ADHD group, the right superior temporal gyrus exhibited an increase in positive functional connectivity, while the left cerebellum showed an increase in negative functional connectivity when compared to controls. There was an artifact in the temporal bone, which was not included in the analysis. Threshold was set at $P < 0.05$.

examined normal adults. This difference may reflect a developmental change in the brain. However, further research is required to clarify the significance of negative functional connectivity and the features of negatively correlated networks associated with the DC in both the immature and adult brains.

Although a reduced volume of the prefrontal cortex has been reported in ADHD [23], the actual role of the prefrontal cortex in ADHD was debatable. Some studies revealed an increased activation of the prefrontal cortex in ADHD during go/no-go task [24] while others reported a decreased activation of the prefrontal cortex in visual selective attention task [25] and in modified flanker task [26]. These controversies may be attributed to many factors such as differences in study approaches, and conditions of the participants (age, gender, medication, and mental status, etc.). Moreover, the prefrontal cortex, even inferior frontal cortex, is a large region containing many sub-regions/nuclei that may have different activities in response to different tasks. With our approaches, we found that ADHD participants indeed exhibited an increase in positive functional connectivity with DC-ROIs in the bilateral inferior frontal gyrus, left superior frontal gyrus and left middle frontal gyrus. Our results indicated that the abnormality in positive functional connections in these regions was responsible for the attention deficit symptoms and impulsive behavior in the patients with ADHD.

Besides the prefrontal cortex, we also found an abnormal positive functional connectivity between the DC and the right superior temporal

gyrus in the ADHD patients. The dysfunction of frontodorsal striatal circuit is likely to be involved in the abnormality of the executive function in ADHD [27]. Rubia et al. [28] reported an abnormality in patients with ADHD in the temporal-striatal networks, suggesting its correlation with inattention symptoms. There were studies showing structural and functional abnormalities of the temporal lobe and functional connectivity between the caudate and temporal lobe in ADHD [29–31].

The cerebellum also participates in the task-negative/default mode network [32]. The default mode network is related to the neural basis of attention dysfunction [8] and the interference of the default mode network and attention network may be a potential mechanism in ADHD [33]. Previous studies revealed a reduction of the cerebellum gray matter volume [34] and a reduction of activation using task-state fMRI [35] in ADHD patients. In this work, we also found an increase of negative functional connectivity in the left cerebellum in the ADHD group. In the children with ADHD, there is a decrease in negative connectivity between ACC and the default mode network [36]. The same is true between the striatum (putamen) and the default mode network [8]. However, Anderson et al. [37] suggest that negative correlations introduced by global signal regression may not exist in the resting state, although other researchers oppose this view [38]. In fact, we found that both the striatum (DC) and the default mode network in ADHD patients exhibited an increased negative connectivity. This increased negative functional connectivity in the patients with ADHD may result from

the dysregulation between default mode network and other brain regions, and may partially account for the symptoms of inattention in ADHD. On the other hand, the inferior frontal gyrus is thought to command vigilance, selective attention, divided attention, and the maintenance of attention [22,39], and is implicated in neuro-pathological basis of ADHD. We found that functional connectivity of the left DC-ROI to the left inferior frontal gyrus exhibited a significant positive correlation with the severity of symptoms of ADHD, suggesting that its dysregulation also contributes to the pathophysiology of ADHD.

5. Conclusion

In conclusion, our data demonstrated that there was connectivity of dorsal caudate with several brain regions in ADHD children and the connectivity of left DC to left inferior frontal gyrus was correlated with severity of ADHD.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

References

- [1] Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics* 2012;3:490–9.
- [2] McLeod KR, Langevin LM, Goodyear BG, Dewey D. Functional connectivity of neural motor networks is disrupted in children with developmental coordination disorder and attention-deficit/hyperactivity disorder. *Neuroimage Clinical* 2014;5:566–75.
- [3] Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, et al. Functional connectivity of human striatum: a resting state fMRI study. *Cereb Cortex* 2008;12:2735–47.
- [4] Grahn JA, Parkinson JA, Owen AM. The cognitive functions of the caudate nucleus. *Prog Neurobiol* 2008;3:141–55.
- [5] Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry* 2005;11:1336–46.
- [6] Overmeyer S, Bullmore ET, Suckling J, Simmons A, Williams SC, Santosh PJ, et al. Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychol Med* 2001;8:1425–35.
- [7] Soliva JC, Fauquet J, Bielsa A, Rovira M, Carmona S, Ramos-Quiroga JA, et al. Quantitative MR analysis of caudate abnormalities in pediatric ADHD: proposal for a diagnostic test. *Psychiatry Res* 2010;3:238–43.
- [8] Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, et al. Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Res* 2009;195–206.
- [9] Hampson M, Peterson BS, Skudlarski P, Gatenby JC, Gore JC. Detection of functional connectivity using temporal correlations in MR images. *Hum Brain Mapp* 2002;4:247–62.
- [10] Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, et al. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol* 2004;4:522–9.
- [11] Cocchi L, Bramati IE, Zalesky A, Furukawa E, Fontenelle LF, Moll J, et al. Altered functional brain connectivity in a non-clinical sample of young adults with attention-deficit/hyperactivity disorder. *J Neurosci* 2012;49:17753–61.
- [12] Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *AJNR Am J Neuroradiol* 2001;7:1326–33.
- [13] Sun L, Cao Q, Long X, Sui M, Cao X, Zhu C, et al. Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Res* 2012;2:120–7.
- [14] Cao J, Wang S, Ren Y, Zhang Y, Cai J, Tu W, et al. Interference control in 6–11 year-old children with and without ADHD: behavioral and ERP study. *Int J Dev Neurosci* 2013;5:342–9.
- [15] Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' parent rating scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;4:257–68.
- [16] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;7:980–8.
- [17] Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995;4:537–41.
- [18] Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci* 2010;13.
- [19] Ledberg A, Akerman S, Roland PE. Estimation of the probabilities of 3D clusters in functional brain images. *NeuroImage* 1998;2:113–28.
- [20] Postuma RB, Dagher A. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb Cortex* 2006;10:1508–21.
- [21] Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 2005;27:9673–8.
- [22] Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 2000;10:475–83.
- [23] Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 1997;3:589–601.
- [24] Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al. Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 2003;10:871–8.
- [25] Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, et al. Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *J Child Psychol Psychiatry* 2005;1:94–111.
- [26] Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;5:439–47.
- [27] Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry* 2005;11:1231–8.
- [28] Rubia K, Smith AB, Brammer MJ, Taylor E. Temporal lobe dysfunction in medication-naïve boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biol Psychiatry* 2007;9:999–1006.
- [29] Tamm L, Menon V, Ringel J, Reiss AL. Event-related fMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2004;11:1430–40.
- [30] Kobel M, Bechtel N, Specht K, Klarhofer M, Weber P, Scheffler K, et al. Structural and functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role? *Psychiatry Res* 2010;3:230–6.
- [31] Vaidya CJ, Bunge SA, Dudukovic NM, Zalecki CA, Elliott GR, Gabrieli JD. Altered neural substrates of cognitive control in childhood ADHD: evidence from functional magnetic resonance imaging. *Am J Psychiatry* 2005;9:1605–13.
- [32] Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, et al. Distinct cerebellar contributions to intrinsic connectivity networks. *J Neurosci* 2009;26:8586–94.
- [33] Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neurosci Biobehav Rev* 2007;7:977–86.
- [34] Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology* 2003;3:496–506.
- [35] Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev* 2007;2:83–91.
- [36] Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2008;3:332–7.
- [37] Anderson JS, Druzgal TJ, Lopez-Larson M, Jeong EK, Desai K, Yurgelun-Todd D. Network anticorrelations, global regression, and phase-shifted soft tissue correction. *Hum Brain Mapp* 2011;6:919–34.
- [38] Chai XJ, Castanon AN, Ongur D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. *NeuroImage* 2012;2:1420–8.
- [39] Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci* 1990;25–42.