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# Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder

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ABSTRACT

A previous study indicated that adults with attention deficit hyperactivity disorder (ADHD) had a decreased anti-correlation between the dorsal anterior cingulate cortex (dACC) and the default mode network (DMN). In this study, we investigated whether children with ADHD also show a decreased anti-correlation between the dACC and the DMN. We also explored the developmental characteristics of the resting-state functional connectivity (RSFC) of the dACC with the DMN in children with ADHD. Resting-state functional magnetic resonance imaging scans were obtained from a 3T scanner in 19 drug-naïve boys with ADHD and 23 controls. Compared with normal controls, the dACC in boys with ADHD showed a significantly decreased negative RSFC with the DMN, including the dorsomedial prefrontal cortex and the posterior cingulate cortex. The RSFC strength between the dACC and the posterior cingulate cortex showed a significantly negative correlation with age in normal controls, but not in boys with ADHD. This decreased anti-correlation may suggest an abnormal balance or interaction between attentional and intrinsic thoughts. Our age-related analysis suggested an abnormal development pattern of the dACC-DMN interaction in ADHD.



## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood, with a prevalence of approximately 5% among school-age children (for review, see Bush et al., 2005). The disorder is characterized by developmentally inappropriate symptoms of inattention, impulsivity and hyperactivity. Although the etiology of ADHD has remained unknown, convergent evidence has implicated fronto-striatal network impairment (for review, see Bush et al., 2005).

The dorsal anterior cingulate cortex (dACC) is an important component of the fronto-striatal circuitry. Many studies have indicated that the dACC plays an important role in the pathology of ADHD. Dysfunction of the dACC could lead to all the cardinal signs of ADHD (see Bush et al., 2005). Structural neuroimaging studies found that both ADHD children and adults had significantly smaller ACC volumes than controls (Carmona et al., 2005; Makris et al., 2007). Functional magnetic resonance imaging (fMRI) studies consistently reported decreased activation in the dACC in subjects with ADHD compared with normal controls in several cognitive tasks, including a Stroop-like paradigm (Bush et al., 1999), Go/No-Go tasks (Tamm et al., 2004) and decision-making tasks (Ernst et al., 2003). Recently, resting-state fMRI studies showed abnormal spontaneous activity in the ACC in children with ADHD (Cao et al., 2006; Castellanos et al., 2008).

The dACC has widespread connections with many other brain regions including the dorsolateral prefrontal cortex (DLPFC), the parietal cortex and the striatum (for review, see Bush et al., 2005). Both cognition and behavior are based on the integrated activity of multiple brain regions, rather than activity in any one isolated region; hence, studying the coupling between regions would seem useful for understanding brain function (Friston, 1994). The relationship between regions can be measured by functional connectivity, which describes the spatiotemporal correlations between spatially distinct brain regions (Friston, 1994). Using this method, Biswal et al. (1995) found that spontaneous low-frequency fluctuations (0.01–0.08 Hz) in resting-state blood oxygenation level-dependent signals within the somatomotor system were highly synchronous and concluded that these were physiologically meaningful. Recently, resting-state functional connectivity (RSFC) MRI has been widely used to characterize the pathophysiological changes of some neurological diseases, disorders such as ADHD (Castellanos et al., 2008; Cao et al., 2009), autism (Di Martino et al., 2009) and Tourette syndrome (Church et al., 2009).

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The default mode network (DMN), first identified by Raichle et al., comprises the medial prefrontal cortex (MPFC), the posterior cingulate cortex (PCC) and the precuneus in the midline of the brain and the bilateral inferior parietal lobule (Raichle et al., 2001). During the resting state, the DMN was found to be negatively correlated with the attentional network (Fox et al., 2005). Many structural and functional neuroimaging studies have demonstrated that components of the DMN are abnormal in ADHD children and ADHD adults (Carmona et al., 2005; Rubia et al., 2005; Makris et al., 2007). Weissman et al. (2006) found that attentional lapses were associated with a decreased negative correlation between the dACC and the DMN in healthy adult volunteers. A recent review by Sonuga-Barke and Castellanos (2007) described the consequent temporally distinctive effects on cognition and behavior of DMN interference into active processing periods. They speculated that the DMN interference was a contributor to ADHD. This hypothesis was tested by their later study, which found that the posterior components (*i.e.*, the precuneus and PCC of the DMN) were less anti-correlated with the dACC in adult ADHD than in controls (Castellanos et al., 2008). We hypothesized that such decreased negative correlation between the dACC and the DMN would also exist in children with ADHD.

Recently, several studies have reported that both the cingulate and the DMN showed distinct age-dependent development of RSFC in healthy volunteers (Fair et al., 2007). Kelly and colleagues reported that healthy adults have a negative relationship between the dACC and the DMN, and that these negatively connected networks are weaker in children and adolescents. They suggested that the significantly age-related shift in the patterns of RSFC associated with the ACC may represent an index of brain maturation (Kelly et al., 2009). Furthermore, Fair et al. (2010) found reduced connectivity within the DMN in ADHD patients compared with age-matched controls. They considered that the atypical connectivity in ADHD may relate to delayed or disrupted maturation. Therefore, our second aim was to perform a preliminary exploration of the developmental characteristics of the brain areas, if any, showing abnormal functional connectivity with the dACC in children with ADHD. Given that the medication history might confound the findings of ADHD-specific neuropathology (Rubia et al., 2005), the current study included drug-naïve patients only.

## 2. Methods

### 2.1. Subjects

Twenty-three drug-naïve boys with ADHD and 25 age-matched healthy boys were included in this study. All the data were from our previous study (Cao et al., 2006) However, in the current study, only drug-naïve boys with ADHD were included in the ADHD group to reduce drug effects. We used the same data as in our previous study (Cao et al., 2009), which explored the resting-state functional connectivity patterns of the putamen in children with and without ADHD. Data from four patients and two normal subjects were excluded because of excessive head motion (see Section 2.3. Data preprocessing). The ages of the remaining subjects were matched for the two groups (ADHD: $n=19$, age: 13.28 (S.D. = 1.35) years; controls: $n=23$, age: 13.20 (S.D. = 0.95) years; $t(40)=-0.22$, $P=0.827$).

All participants were between 11 and 16 years. All the subjects 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 severe disease; 4) no history of psychiatric disorders including schizophrenia, affective disorder and pervasive developmental disorder; 5) scores of higher than 80 on the Wechsler Intelligence Scale for Chinese Children — Revised (Gong and Cai, 1993).

ADHD children were recruited from the juvenile psychiatric clinic at the Institute of Mental Health, Peking University. Inclusion in the ADHD group was based on separate clinical assessments by two pediatric psychiatrists, one of whom was a senior psychiatrist. Diagnostic criteria were derived from the Clinical Diagnostic Interviewing Scales (CDIS) (Barkley, 1998), a structured and interviewer-administered scale based on DSM-IV (American Psychiatric Association, 1994). The CDIS is composed of questions about behavioral and emotional disorders of childhood, such as ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), tic disorder, emotional disorder, affective disorder, anxiety, and obsessive-compulsive disorder. The ADHD Rating Scale — IV (ADHD RS-IV) was obtained from parents to assess the presence and severity of ADHD symptoms. The ADHD RS-IV contains all the inattention and hyperactivity/impulsivity symptoms of ADHD according to DSM-IV. Each symptom is scored according to how often it occurs (*i.e.*, "never" is rated as 1, "occasionally" is 2; "often" is 3; and "always" is 4).

ADHD patients with comorbid CD or ODD were not excluded. Twelve patients met criteria for the ADHD-I subtype (the predominantly inattentive subtype; two of these had comorbid ODD, one had comorbid CD) and seven for the ADHD-C subtype (the combined subtype; three of these had comorbid ODD, one had comorbid CD).

The controls came from local schools near the Institute of Mental Health, Peking University. They were also screened by the same psychiatrists using the CDIS.

This study was approved by the Research Ethics Review Board of the Institute of Mental Health, Peking University. After a complete description of the study procedures, written informed consent was obtained from parents or guardians of the subjects. All children agreed to participate.

### 2.2. Imaging procedures

MRI data were acquired using a 3T SIEMENS Trio scanner (Siemens Medical Solutions, Erlangen, Germany) in the Institute of Biophysics, Chinese Academy of Sciences. In addition to resting-state fMRI and 3D structural MRI, there were task-state fMRI and diffusion tensor imaging scanning sessions (Cao et al., 2008, 2010). The parameters for the resting-state fMRI were as follows: 30 axial slices, echo-planar imaging pulse sequence, thickness/gap = 4.5/0 mm, in-plane resolution = $64\times64$, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = $220\times220$ mm, 240 volumes. The subjects were asked to keep still as far as possible, keep their eyes closed, and try not to think of anything in particular during the resting-state fMRI scanning.

Our data were collected over a period of approximately 2 years and some modifications were made to the parameters for the 3D structural images. Among the 42 subjects (19 ADHD and 23 controls) included in the statistical analysis, four sets of parameters for the 3D T1-weighted structural images were used, as shown in Table 1. However, only two of the parameter sets were used for 40 of the 42 subjects. In addition, the proportion of the number of subjects using the two sets of parameters was similar for ADHD patients and normal controls. The 3D images were used for spatial normalization (see Section 2.3. Data preprocessing).

### 2.3. Data preprocessing

The first 10 volumes were discarded for scanner calibration and for subjects' adaptation to the scanner noise. Part of the data preprocessing was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm), including slice timing and head motion correction (a least squares approach and a

**Table 1**
Parameters for 3D T1-weighted images.

| Parameters | P1 | P2 | P3 | P4 |
|---|---|---|---|---|
| TR (ms) | 845 | 2000 | 1770 | 1950 |
| TE (ms) | 2.89 | 3.67 | 3.92 | 2.60 |
| Flip Angle (°) | 8 | 12 | 10 | 12 |
| FOV (mm) | 261×261 | 256×256 | 256×256 | 240×256 |
| Thickness/gap (mm) | 1/0 | 1/0 | 1.3/0 | 1.33/0 |
| Number of subjects | P: 12, C: 8 | P: 9, C: 11 | P: 1 | P: 1 |

P1–P4: 4 sets of parameters; TR: repetition time; TE: echo time; FOV: field of view; Number of subjects: P denotes patient and C denotes control subjects.

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six-parameter spatial transformation). Data from four patients and two normal subjects were excluded because of excessive head motion (more than 3 mm of translation or more than 3° of rotation in any direction). The fMRI data were spatially normalized to the Montreal Neurological Institute (MNI) template (resampled voxel size = 3 × 3 × 3 $mm^3$) *via* the gray matter obtained from 3D images as follows. The individual 3D structural image was co-registered to the fMRI data and then segmented into gray matter, white matter and cerebrospinal fluid. Then the individual gray matter image was spatially normalized to the MNI gray matter template and the transformation matrix was also used on the fMRI data. This segmentation procedure was used to improve the accuracy of spatial normalization (Ashburner and Friston, 2005). The fMRI data were spatially smoothed (full width at half maximum = 4 mm). An in-house software Resting-State fMRI Data Analysis Toolkit (REST; http://www.restmri.net) was then used for removing the linear trend of the time series and temporal band-pass filtering (0.01–0.08 Hz) (Biswal et al., 1995).

### 2.4. Functional connectivity analysis

The seed region of interest (ROI) in the current study approximates the location of the bilateral dACC defined in a previous review (Bush et al., 2000) and in a previous study (Tian et al., 2006). The detailed definition procedures were as follows. The bilateral dACC was extracted from the automated anatomical labeling template (Tzourio-Mazoyer et al., 2002) from MRIcro software (http://www.cabiatl.com/mricro/) (Fig. 1). The anterior border of the dACC-ROI was defined as the coronal plane crossing the most anterior edge of the corpus callosum. The posterior border of the dACC-ROI was defined as the coronal plane crossing the anterior commissure (Bush et al., 2000) (Fig. 1). This ROI was re-sampled to voxel size = 3 × 3 × 3 $mm^3$. Subsequent data processing was performed using REST software. The time courses within this ROI were averaged to generate a reference time course for each subject. Pearson's correlation analysis was performed between the seed reference time course and the time series of each voxel in the brain in a voxel-wise manner, with the global mean time course, the white matter mean time course, the cerebrospinal fluid mean time course and the six head motion parameters as nuisance covariates. Individual correlation coefficients were converted to *z*-scores using Fisher's transformation to improve the normality.

### 2.5. Statistical analysis

#### 2.5.1. Within-group connectivity of the dACC

One-sample *t*-tests were performed on the *z*-maps of boys with ADHD and controls, respectively. Voxels with $P<0.05$ and cluster size > 1485 $mm^3$ were taken as being significantly connected to the dACC. Such a combination corresponds to $P<0.05$ after correction for multiple comparisons using Monte Carlo simulation (AlphaSim in AFNI software; http://afni.nimh.nih.gov).

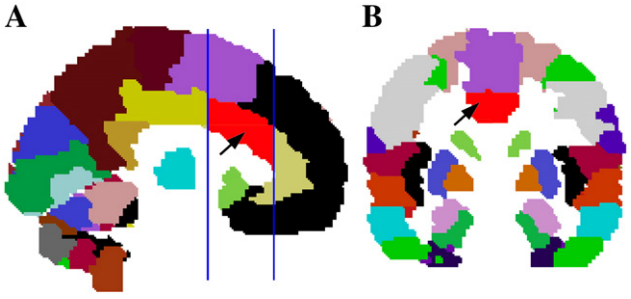


**Fig. 1.** The dACC-ROI (black arrow in the sagittal view (A) and coronal view (B)) was defined based on the automated anatomical labeling template implemented in MRIcro software. The vertical blue lines indicate the anterior and posterior borderlines, respectively, of the dACC. Please see 2.4 Functional connectivity analysis in the Methods for details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

#### 2.5.2. Between-group differences in connectivity of the dACC

Voxels surviving the combination criteria in either the ADHD group or the control group formed a union mask, in which the surviving voxels have significant functional connectivity to the dACC in at least one group. A recent resting-state fMRI study showed that IQ correlated with spontaneous activity (Song et al., 2008). Therefore, to reduce the potential confounding effect of IQ, we used IQ as a covariate when performing the two-sample *t*-test. The two-sample *t*-test was implemented using the 3dRegAna program in AFNI software. Voxels with $P<0.01$ and cluster size > 324 $mm^3$ (12 voxels) were taken as being significantly different between the two groups in functional connectivity to the dACC. Such a combination corresponds to $P<0.05$ after correction for multiple comparisons using Monte Carlo simulation (using AlphaSim).

All the results were overlaid on a structural image in MRIcro software and converted to Talairach and Tournoux coordinates (Talairach and Tournoux, 1988).

#### 2.5.3. Exploratory correlation between the connectivity of the dACC and age

To investigate the development of functional connectivity of the dACC, exploratory correlation analyses were performed between the mean *z*-scores of each cluster and the age of each group.

## 3. Results

### 3.1. Demographic information and standardized tests

As shown in Table 2, there was no significant difference between the two groups in terms of age ($t$ (40) = −0.220, $P=0.827$). The mean IQ of the controls was higher than that of the ADHD subjects ($t$ (40) = −2.976, $P=0.005$). Compared with the controls, the ADHD group obtained higher scores in the ADHD RS-IV ($t$ (40) = −8.094, $P=1.270\times10^{-9}$).

### 3.2. Within-group connectivity patterns of the dACC

One-sample *t*-tests within the control group showed that the dACC had a positively correlated network as well as a negatively correlated network (Fig. 2A). The functional connectivity patterns were very similar in the right and left hemispheres. The positive network consisted of the DLPFC, the basal ganglia, the insula, the superior and middle temporal gyri, the supplementary motor area, the middle cingulate cortex and the anterior part of the cerebellum. The negative network included the PCC, the precuneus, the MPFC, the bilateral inferior parietal lobule, the hippocampi, and the bilateral hemispheres. Most of the negatively correlated regions are within the DMN. In spite of the significant between-group difference (see Section 3.3 below), by visual

**Table 2**
Demographic information and standardized test results.

| Variables/group | ADHD ($n=19$) mean (S.D.) | Controls ($n=23$) mean (S.D.) | $t$ | $P$ |
|---|---|---|---|---|
| Age (years) | 13.28 (1.35) | 13.20 (0.95) | −0.220 | 0.827 |
| Full-scale IQ | 102.68 (10.37) | 113.52 (12.77) | 2.976 | 0.005 |
| *ADHD RS-IV* | | | | |
| Inattention | 27.72 (4.39) | 15.85 (4.98) | −7.761 | $3.388\times10^{-9}$ |
| Hyperactivity/impulsivity | 22.56 (6.63) | 12.40 (2.26) | −6.459 | $1.702\times10^{-7}$ |
| Total scores | 50.28 (9.42) | 28.42 (6.70) | −8.094 | $1.270\times10^{-9}$ |

Note: ADHD = attention deficit/hyperactivity disorder; ADHD RS-IV: ADHD Rating Scale — IV.

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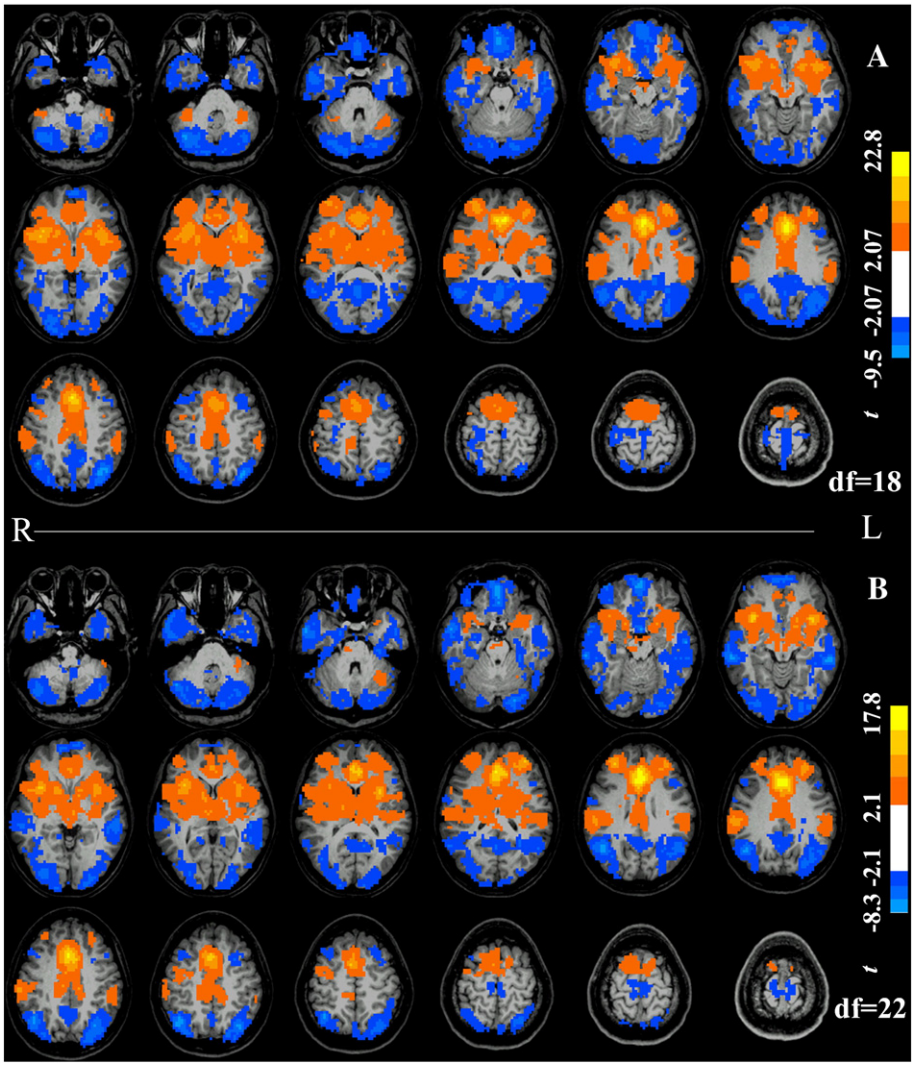


**Fig. 2.** Results of one-sample *t*-tests of the dACC connectivity patterns in the control group (A) and the ADHD group (B). The 18 slices are from −35.5 to +66.5 mm (*z* coordinates in the Talairach and Tournoux system) in a step of 6 mm. Yellow indicates positive functional connectivity and *vice versa* for the blue color. L: left; R: right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

inspection, the pattern of functional connectivity of the dACC for the ADHD group (Fig. 2B) was similar to that of the control group.

### 3.3. Between-group connectivity differences

Compared with the normal controls, the dACC in boys with ADHD showed decreased negative functional connectivity with the dorsomedial prefrontal cortex (DMPFC) (Brodmann areas (BA) 9 and 10) ($P<0.05$, corrected) and the PCC (BA 29, 30) ($P<0.05$, corrected); the latter extending to the adjacent retrosplenial cortex (BA 29, 30) and lingual gyri (BA 18) ($P<0.05$, corrected) (Table 3, Fig. 3). In detail, all of these brain areas showed significant negative connectivity with the dACC in normal controls (Table 3), while the functional connectivity with the dACC was not significant ($P>0.05$), *i.e.*, no functional connectivity exists, in ADHD subjects. The left middle temporal gyrus (MTG) also showed a significant between-group difference in functional connectivity with the dACC ($P<0.05$, corrected). In detail, the left MTG showed no significant functional connectivity with the dACC in normal controls, while it showed significant negative functional connectivity in ADHD subjects (Table 3, Fig. 3).

Furthermore, in order to clarify whether age had a significant effect on the group differences in functional connectivity with the dACC, we also used age as a covariate when performing the statistical analysis on the clusters showing significant differences. Compared with the normal controls, the dACC in boys with ADHD still showed decreased negative functional connectivity with the DMPFC ($F(1, 39) = 13.606$, $P = 0.001$) and the PCC ($F(1, 39) = 16.361$, $P = 0.0002$); the latter extending to the adjacent retrosplenial cortex and lingual gyri ($F(1, 39) = 13.207$,

**Table 3**
Brain areas with significant differences in the functional connectivity of the dACC between ADHD subjects and normal controls.

| Brain region | BA | Controls ($n=23$) Mean (S.D.) | ADHD ($n=19$) Mean (S.D.) | Volume ($mm^3$) | Coordinates ($x$, $y$, $z$) | $t$-value | $P$-value |
|---|---|---|---|---|---|---|---|
| Left RSC, left LG | 30/29/18 | −0.091 (0.13) | 0.054 (0.125) | 810 | −8, −53, 6 | −3.619 | 0.001 |
| Left DMPFC | 9/10 | −0.149 (0.162) | 0.025 (0.124) | 675 | −8, 53, 30 | −3.726 | 0.001 |
| Right PCC | 29/30 | −0.113 (0.140) | 0.051 (0.137) | 432 | 5, −56, 9 | −3.830 | 0.0004 |
| Right MTG | 21/22 | −0.004 (0.156) | −0.146 (0.175) | 405 | −50, −47, 3 | 2.855 | 0.007 |

RSC: retrosplenial cortex; LG, lingual gyrus; DMPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; MTG, middle temporal gyrus; BA, Brodmann's area.

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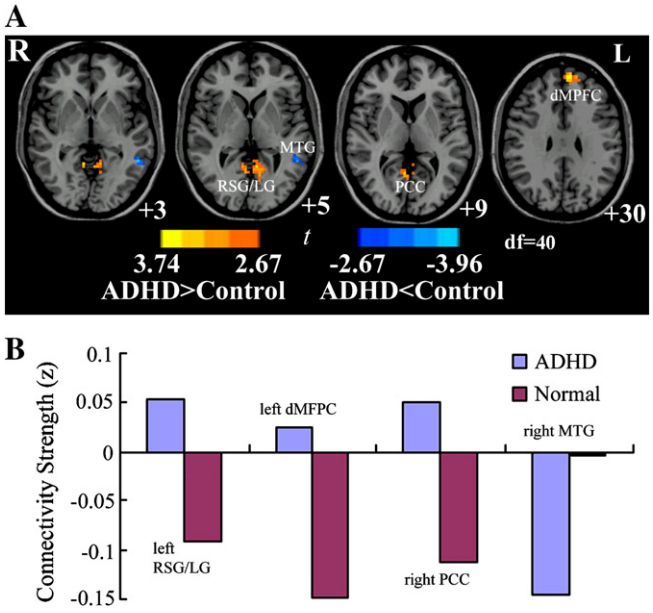


**Fig. 3.** Results of two-sample *t*-tests on the functional connectivity of the dACC. (A) Yellow color (including the PCC and the DMPFC) indicates increased functional connectivity with the dACC in the ADHD group and *vice versa* for the blue color (the left MTG). (B) In the left RSG/LG, the left DMPFC and right PCC, normal controls showed significantly negative functional connectivity ($P<0.05$), but ADHD subjects showed no significant connectivity ($P>0.05$). In the right MTG, children with ADHD showed significantly negative functional connectivity, but normal controls showed no significant connectivity. See Table 3 for more details. ADHD: attention deficit hyperactivity disorder; RSG: retrosplenial gyrus; LG, lingual gyrus; DMPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; MTG, middle temporal gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$P=0.001$). The left MTG also showed a significant between-group difference in functional connectivity with the dACC ($F(1, 39)=7.900$, $P=0.008$). Therefore, in our study, age had no significant effect on the results.

### 3.4. Correlation analysis of connectivity of the dACC with age

Correlation analysis was performed between the connectivity strength (*i.e.*, the mean *z*-value of each cluster) of the brain regions showing group differences and the age for each group separately. The age and strength of functional connectivity of the dACC to the PCC showed a significant negative correlation ($r=-0.463$, $P=0.026$) in normal controls, but not in boys with ADHD ($r=-0.183$, $P=0.454$) (Fig. 4). No other significant correlation between age and connectivity strength was found.

## 4. Discussion

In the current study, we analyzed the intrinsic functional connectivity patterns of the dACC in drug-naïve boys with ADHD and healthy controls, and explored the correlation between the age and connectivity strength of the dACC. Our findings were consistent with, and expanded upon, observations from a previous study of adults with ADHD (Castellanos et al., 2008). On the whole, the functional connectivity patterns in ADHD subjects were similar to those of controls. In the control group, the positive network consisted of the DLPFC, the basal ganglia, the insula, the superior and middle temporal gyri, the supplementary motor area, the middle cingulate cortex, and the anterior part of the cerebellum. The negative network included the PCC, the precuneus, the MPFC, the inferior parietal lobule, and the bilateral cerebellar hemisphere. Most of the anti-correlated regions were within the DMN. These results are consistent with the results of previous anatomical and functional neuroimaging studies (Vogt et al., 1995; Margulies et al., 2007).

In the between-group analysis, the PCC (including its adjacent retrosplenial cortex and lingual gyrus) and DMPFC showed significantly decreased negative connectivity with the dACC in ADHD subjects. In normal controls only, the age and connectivity strength of the dACC were significantly negatively correlated, *i.e.*, as the children grow older, the anti-correlation between the dACC and the PCC becomes stronger.

We found that the PCC showed disrupted connectivity to the dACC in ADHD subjects. The PCC, an important component of the DMN, is associated with an introspective attentional orientation related to mentalizing and emotional processing during rest (Buckner et al., 2008). Recently, the PCC has been receiving increasing attention in the ADHD neuroimaging literature. Studies of children and adolescents with ADHD using whole-brain voxel-based morphometry have identified gray matter volume reduction in the PCC (Carmona et al., 2005; Makris et al., 2007). Several task-based fMRI studies found that adolescents with ADHD showed abnormal activation in the PCC, which was negatively correlated with ADHD symptom severity (Rubia et al., 2005; Silk et al., 2005). In addition, during high-order motor control tasks, both the ACC and PCC showed decreased activation in adolescents of the ADHD group

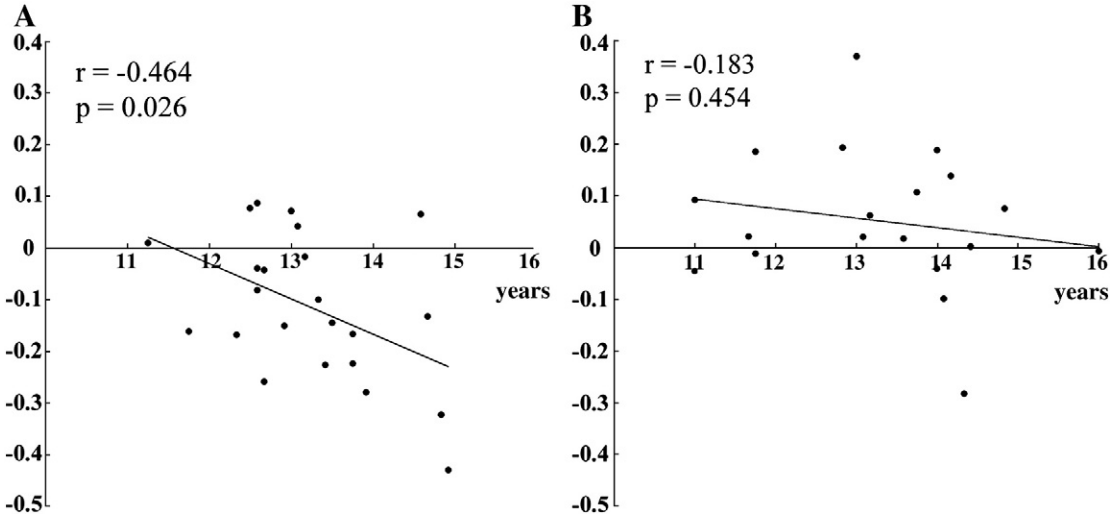


**Fig. 4.** Plots displaying the correlation between the connectivity strength (the *z*-value, *y* axis) and age (*x* axis) in the posterior cingulate cortex of each group (A: control group; B: ADHD group).

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(Rubia et al., 1999). Fransson (2006) found that a suppression and a reorganization of intrinsic network activity occur in response to an attention-demanding task, and confirmed that spontaneous intrinsic activity in the DMN is attenuated during performance of a working memory task. Weissman et al. (2006) reported that momentary lapses in attention are associated with both reduced activity in the frontal control regions (the dACC) and greater activity (that is, failure to suppress activity) in the DMN (including the PCC and precuneus), suggesting an imbalance in the fronto-DMN in this condition. Therefore, Sonuga-Barke and Castellanos (2007) hypothesized that fronto-DMN interactions may represent a novel locus of dysfunction in ADHD, which could potentially account for the ADHD-related increases in intrasubject variability. Subsequently, Castellanos et al. (2008) confirmed that ADHD in adults is also associated with abnormalities in the dACC-PCC connectivity. They interpreted their findings that the long-range connection linking the dACC to the PCC should be considered a candidate locus of dysfunction in ADHD (Castellanos et al., 2008). Our findings were consistent with these. In addition, using the same data, our previous study found decreased negative functional connectivity between the putamen and the regions in the DMN in children with ADHD. It also suggested that the impairment of the balance between the DMN and other regions in the brain may underlie the pathological basis of ADHD (Cao et al., 2009). Given that many studies have indicated that adults and children with ADHD share similar clinical features, neuropsychological deficits and failures in major life domains (Faraone et al., 2000), combination of the results of the current study of children with those of the earlier study of adults (Castellanos et al., 2008) suggests that a disconnection between the dACC and the PCC may exist in children with ADHD and persist into adulthood.

Similar to the PCC, the DMPFC is also a "core hub" in the DMN, which is associated with introspective orientated thought (Buckner et al., 2008). There is evidence indicating functional or structural abnormalities of the DMPFC in ADHD subjects. Rubia et al. (2010) reported that ADHD boys showed reduced activation compared with healthy control children in the right DMPFC. Fassbender et al. found that children with ADHD displayed significantly more reaction time variability and less deactivation in the MPFC than controls during a working memory paradigm (Fassbender et al., 2009). Moreover, the increased variability in reaction time was also related to abnormal activation in the ACC in adolescents with ADHD (Rubia et al., 2007). Our research indicated the abnormal relationship between the ACC and the DMPFC. Hence, decreased functional connectivity between the dACC and the MPFC may play a role in the pathophysiological mechanisms of ADHD in children.

However, Castellanos et al. (2008) did not find decreased functional connectivity between the dACC and the DMPFC. Shaw et al. (2007) reported that the ADHD group ($10.2 \pm 3.2$ years) displayed development of the MPFC that was later than in normal children, lagging behind 5 years in terms of it reaching its cortical peak thickness. This suggests that the age difference may, at least in part, explain the differences between Castellanos et al.'s conclusions and our own. A study by Kelly et al. (2009) used a unidirectional assumption of decrease or increase between three groups, *i.e.*, children > adolescents > adults, or children - adolescents < adults. They found that the anti-correlation between the dACC and the dMPFC in the DMN increased with age. This suggests that the abnormal functional connectivity of the dACC with the MPFC in children with ADHD may be normalized in adulthood. However, the age-related changes in functional connectivity between the dACC and the MPFC in Kelly et al.'s study were obtained by group comparison. Group comparison does provide a difference between groups but does not provide within-group information. In other words, it is unclear whether there is a linear correlation between the functional connectivity strength of the dACC-DMPFC and age in children. The current study did not find a significant linear correlation in either the ADHD or the control group. However, our sample size may be too small to depict a developmental trajectory.

In the current study, the left MTG showed a significant difference in connectivity with the dACC between the children with ADHD and the healthy boys. There is evidence for structural (Kobel et al., 2010) and functional (Shafritz et al., 2004; Tamm et al., 2004) abnormalities in the temporal lobe in ADHD. Kobel et al. (2010) found that boys with ADHD showed smaller gray matter volumes and decreased magnetization transfer imaging values in the temporal lobe. They speculated that the temporal lobe might play a key role in the etiology of ADHD. During the divided attention task, adolescents with ADHD showed significantly less activation in the middle temporal gyrus than the comparison subjects, and only the left middle temporal lobe activation was correlated with accuracy on the visual selective tasks (Shafritz et al., 2004). Furthermore, Tamm and colleagues found that, compared with the control subjects, adolescents with ADHD showed increased activation in the left MTG while decreased activation was found in the dACC (Tamm et al., 2004). The authors proposed an involvement of the frontotemporal circuitry in aberrant response inhibition and task switching in ADHD (Tamm et al., 2004). To some extent, the inverse activation patterns in the left MTG and dACC in that study seem to be consistent with the current result of abnormal negative connectivity between the two brain areas. So far, interpretation of the abnormal connectivity between the dACC and the MTG remains uncertain. Further investigation of the interaction between the left MTG and the dACC in ADHD is needed, and this finding requires replication.

In the present study, we found that the strength of the anti-correlation between the dACC and the PCC increased with age in the normal children. However, in the ADHD group, the anti-correlation was weakened and there was no linear relationship with age. This showed that the children with ADHD have abnormal development patterns for the dACC–DMN interaction. It is unclear whether ADHD results from a delay in brain maturation or whether it represents a complete deviation from the template of typical development. Several functional imaging studies have found that ADHD indicates a developmental deviation rather than a maturational lag in the central nervous system (Clarke et al., 2001; Hobbs et al., 2007). Our findings are in line with the results mentioned above. However, using structural imaging studies, Shaw et al. (2007) and Castellanos et al. (2002) found that the development of the cortical thickness and regional cerebral volumes in children with ADHD lagged behind those of typically developing children by several years, but that the maturational process proceeded normally (with the potential for later "catch up"). We believe that a simple "delay-only" or "deviation-only" paradigm will likely be insufficient to describe ADHD populations fully. It is possible that the developmental trajectories of the brain function and structure are not parallel in ADHD, although the delayed structural maturation of the brain in ADHD subjects becomes normalized with age. However, the integrated pattern or the interaction of multiple brain regions in ADHD subjects may remain different from those in normal controls. This might explain why up to 80% of ADHD children continue to experience symptoms in later life. From a functional connectivity point of view, our findings imply that abnormal development of the dACC–DMN interaction is involved in the pathogenesis of ADHD. This study is the first to explore the developmental characteristics of RSFC of the dACC with the DMN in children and adolescents with ADHD. Further studies are needed to establish the validity of our results.

Several issues in the present study should be noted. Firstly, we regressed out the global mean signal when performing functional connectivity analysis, as is done in most functional connectivity studies (*e.g.*, Fox et al., 2005; Castellanos et al., 2008; Kelly et al., 2009). However, the global trend was not taken as a nuisance covariate in a previous ADHD study (Tian et al., 2006), in which an increased positive functional connectivity between the dACC and the PCC was found in ADHD children, and the antiphase relationships were not different. No other brain regions in the DMN displayed abnormal connectivity with the dACC in that study (Tian et al., 2006). A recent study suggested that removal of the global

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mean signal is the most likely cause of anti-correlation (Murphy et al., 2009). Therefore, it is likely that removal of the global mean signal may account for the discrepancy between our results and those of Tian et al. and Castellanos et al. (2008). Examining the effect of removing or not removing the global trend will provide more information from a methodological point of view. However, in addition, the subject population of the current study was very different from that used in Tian et al. (2006). Some discrepancies between the results would be expected even without removing the global trend. We support that an abnormal anti-correlation between the external attentional system and the internal intrinsic thought system is a plausible interpretation of ADHD from a pathopsychological point of view (Sonuga-Barke and Castellanos, 2007). However, further studies on the effect of the global mean signal are needed. Secondly, the current study included two subtypes of ADHD (12 subjects with ADHD-I and 7 with ADHD-C). The two subtypes were not analyzed separately because of the relatively small sample size. Future studies with well-defined patient populations will better elucidate the characteristics of the ADHD subtypes.

In recent years, our group has collected a cohort of RS-fMRI dataset including about 32 boys with ADHD and 28 control boys. Using various analytic approaches commonly used in the community of RS-fMRI, our collaborative groups have had a few publications on this dataset (or subset). This dataset is freely available now (http://fcon_1000.projects.nitrc.org/indi/adhd200/). These analytic approaches included linear correlation based functional connectivity (Tian et al., 2006; Cao et al., 2009), regional homogeneity (Cao et al., 2006), amplitude of low frequency fluctuation (Zang et al., 2007), small world complex network analysis (Wang et al., 2009), and Fisher discriminative analysis (Zhu et al., 2008). In addition, a structural study has also been implemented on this dataset to measure the area and white matter integrity of the corpus callosum (Cao et al., 2010). However, few studies have investigated the relationship of these methods. Even for the linear correlation-based functional connectivity analysis, different seed ROIs will yield very different connectivity patterns (Tian et al., 2006; Cao et al., 2009). It should be critical for future methodological studies to reveal the relationships among these methods. This will help to understand the ADHD pathophysiology from various aspects (please see Supplementary electronic material).

In summary, our current resting-state fMRI study found a decreased anti-correlation between the dACC and the DMN in boys with ADHD compared with control boys. The present finding is in line with the hypothesis that ADHD is associated with abnormalities in fronto-default mode interactions (Sonuga-Barke and Castellanos, 2007). This decreased anti-correlation may suggest an abnormal balance or interaction between attentional and intrinsic thoughts. Our age-related analysis suggests a deviation in normal development of the dACC–DMN interaction in ADHD.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.pscychresns.2011.07.001.

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