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ORIGINAL RESEARCH

Asymmetry in Cortical and Subcortical Structures of the Brain in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

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Background: Human cognitive and emotional functions are asymmetrical between the left and right hemispheres. In neuroimaging studies of attention-deficit/hyperactivity disorder (ADHD) patients, the absence of aberrant asymmetry might serve as a neuroanatomical marker of ADHD. However, few studies have estimated abnormalities in cortical and subcortical asymmetry in children and adolescents of different ADHD subtypes.

Methods: Data were from the results collected by the Peking University site in the "ADHD-200 sample" dataset, which comprised 31 eligible ADHD (20 inattentive ADHD (ADHD-I), 11 combined ADHD (ADHD-C)) and 31 matched typically developing (TD) individuals. The Asymmetry Indexes (AIs) in cortical thickness, cortical gray-matter volume and subcortical nucleus (SN) volume were calculated based on an automated surface-based approach. The differences in cortical thickness, cortical gray-matter volume, and SN volume AIs were evaluated among groups. We also analyzed the correlation between AIs and the severity of ADHD symptoms.

Results: Compared with the TD group, SN asymmetry in ADHD group did not reveal significant differences. Altered cortical asymmetry of different subtypes in ADHD groups was located in the orbitofrontal and anterior cingulate circuits, including the medial orbitofrontal, paracentral, pars triangularis, caudal anterior cingulate, isthmus cingulate, and superior frontal regions. In the comparisons, cortical gray-matter volume AIs were significantly different in the caudal anterior cingulate, isthmus cingulate, and superior frontal regions between ADHD-I and ADHD-C groups. There were significant correlations between the severity of ADHD symptoms and asymmetric measurements in medial orbitofrontal, paracentral and isthmus cingulate regions.

Conclusion: These findings provide further evidence for the altered cortical morphological asymmetry in children and adolescents with ADHD, and these differences are associated (at least in part) with the severity of ADHD symptoms. Brain asymmetry could be an appropriate precursor of morphological alterations in neurodevelopmental disorders.

Keywords: attention-deficit/hyperactivity disorder, child and adolescent, cortical and subcortical, asymmetry

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder. It can affect the health and social function of children and adolescents to a large extent. The core deficits of ADHD are associated with controlled processes and executive functions, and executive deficits might be due (at least in part) to impairment in automatic processing.[1,2] According to the Diagnostic and

Statistical Manual of Mental Disorders, Fourth Edition, ADHD can be divided into three subtypes on the basis of the predominant symptomatology: the inattentive (ADHD-I), the hyperactive/impulsive (ADHD-HI) or the combined ADHD (ADHD-C) subtypes.[3,4] The worldwide prevalence of ADHD is about 5.0–7.1%,[4] and the prevalence of ADHD-I is the highest, followed by ADHD-C.[5] The course of ADHD is usually chronic. The lifelong prevalence of ADHD can reach up to 15%,[6] which is closely associated with a high prevalence of recurrence and low compliance of children and adolescents with ADHD. Such a high lifelong prevalence of ADHD imposes a heavy burden upon society. Therefore, exploring further the pathogenesis of this neurodevelopmental disorder is becoming increasingly important.

Brain hemispheres have asymmetric characteristics in terms of structure and function.[7] The dominant hemisphere for verbal cognitive function is the left hemisphere. The dominant hemisphere for spatial cognitive function is the right hemisphere. The most widely identified structurally asymmetric regions are the right-lateralization of the frontal lobe and left-lateralization of the occipital lobe.[8,9] Studies have shown that changes in the asymmetry of the brain are associated with the sex, age, handedness, and neuropsychiatric disorders of individuals (eg, schizophrenia,[10] major depressive disorder,[11] and Alzheimer's disease).[12] The absence of asymmetry in healthy people might serve as a neuroanatomical marker of neurodevelopmental disorders (especially ADHD).[10,13]

Numerous studies on the anatomic and functional differences in the brains of people suffering from ADHD have been carried out. A meta-analysis of the studies based on voxel-based morphometry reported a reduction in the gray-matter volume in the caudate and putamen of ADHD patients.[14] A recent cross-sectional study explored if ADHD patients had smaller gray-matter volume in the amygdala, caudate, hippocampus, and putamen.[15] Some functional magnetic resonance imaging (fMRI) studies have demonstrated that patients with ADHD have structural and functional abnormalities in cortico-striatal circuits.[16,17] Abnormalities in these brain regions damage the cognitive functions of individuals, such as the abilities of attention, automatic processing, and executive monitoring.[2,18] Silk and colleagues, using diffusion tensor imaging, showed that an ADHD group had anomalous hemispheric asymmetry in the fiber tracts of the fronto-striatal system. ADHD patients did not have the right-lateralization of tract connections between the caudate and prefrontal cortex observed in typically developing (TD) controls.[19] Therefore, the subcortical nucleus (SN) might play a unique part as a precursor of more distinct asymmetry in the human brain. Studies have mostly analyzed alterations in the gray-matter volume from a voxel-based perspective,[4,14,20–22] which may underestimate subtle differences in cortical structure. The cortical gray-matter volume is affected by several factors, such as surface area, thickness, and folding of the cortex. In contrast, cortical thickness (another commonly used measure of the cortex) could be more sensitive to disorder-related structural differences in the human brain.[23] However, only one surface-based analysis has investigated the hemispheric asymmetry in young patients with ADHD.[24] Moreover, no one has estimated whether and how different ADHD subtypes could affect the hemispheric asymmetry of cortical and subcortical structures of the brain.

Our study had two main aims. The first aim was to investigate the subcortical structural asymmetry as a potential subcortical precursor in children and adolescents with ADHD. Second, we assessed whether ADHD subtypes might influence the asymmetry of cortical and subcortical structures, and the association between these cortical and subcortical asymmetric alterations and symptoms in patients with ADHD.

Materials and Methods

Participants

The data of our study were from the "The ADHD-200 sample" dataset[25] in the "1000 Functional Connections Project" project group. All data in the present study were from the results collected by the Peking University (Beijing, China) site, which included the brain imaging of children. We did not choose multi-site data so as to avoid the adverse effects of the collection equipment and environment of different sites on the results. In the database of the Peking University site, patients were recruited from the Outpatients Department of the Institute of Mental Health of Peking University. TD individuals were children and adolescents recruited from nearby schools who did not have a current or previous psychiatric diagnosis or known neurological disorder. All participants in our study were right-handed with an intelligence quotient (IQ) score >80. Patients with neurological disorders, neurodevelopmental disorders, schizophrenia, affective disorders, oppositional defiant disorders, and learning disorders were excluded. The database recorded only whether participants had

medications but lacked detailed information on how long ago or whether ADHD participants had taken them recently. Hence, we did not exclude ADHD participants who were taking medications (seven cases with ADHD-I and five ADHD-C cases were not medication-naïve). All data from the Peking University site were approved by the Research Ethics Review Board of the Institute of Mental Health within Peking University. One parent of each participant and all children provided written informed consent before participating. The guidelines outlined in the Declaration of Helsinki 1964 and its later amendments were followed in the present study. All structural magnetic resonance imaging (sMRI) data and demographic data were complete and usable. Finally, 31 eligible samples of ADHD data (20 ADHD-I and 11 ADHD-C) were obtained, and data samples from 31 matched (age, sex, and IQ score) TD individuals were collected.

All participants were interviewed with the Schedule of Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[26] and full-scale Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R).[27] The ADHD Rating Scale (ADHD-RS) IV[28] was employed to measure ADHD symptoms.

MRI Analysis

Before further analyses of brain images, we first confirmed that all sMRI scans downloaded from the database were unaffected by head movement or other artifacts to ensure the image quality. sMRI scans were processed automatically with the FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) recon-all processing pipeline for whole-brain cortical morphological characteristics. After that, the processing results of each participant were checked and corrected manually. The SN includes the thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens.

Statistical Analysis

Data were analyzed using SPSS 20.0 (IBM, Armonk, NY, USA). The two-sample *t*-test was employed for the parameters of two independent groups with a normal distribution (eg, age, IQ score, ADHD-RS IV score). The Mann–Whitney U-test was used for data with a non-normal distribution. The one-way ANOVA test was undertaken for the parameters of multiple groups that had a normal distribution. The Kruskal–Wallis H-test was employed for the parameters of multiple independent groups with a non-normal distribution. The chi-square test was used to compare sex distribution. The difference between the left and right hemispheres of each cortical and subcortical region was represented by the Asymmetry Index (AI):

$$AI = (L - R/L + R) \times 100$$

where L is the value for the left hemisphere, R is the value for the right hemisphere, and the AI ranges from −100 (complete rightward asymmetry) to +100 (complete leftward asymmetry). The Kruskal–Wallis H-test was employed to compare the differences in the AIs for the volume of the SN between children and adolescents with different ADHD subtypes and that in TD controls. Simultaneously, according to the Desikan–Killiany template, each hemisphere of the cortical regions was divided into 34 regions. The Mann–Whitney and Kruskal–Wallis tests were used to evaluate the differences in the average cortical thickness AI and gray volume AI of each region. Finally, the correlation between the AIs and clinical characteristics of ADHD patients was analyzed.

Results

Demographic and Clinical Characteristics

Data for demographic characteristics and clinical characteristics for ADHD and TD groups are shown in Table 1a. The results of the two-sample *t*-test and chi-square test showed that there were no significant differences in age, sex, or IQ score between the two groups ($P > 0.05$). The severity of ADHD symptoms (subscale scores of ADHD-RS IV) was significantly different between the two groups ($P < 0.05$). The subscale scores were higher in ADHD patients compared with those in TD participants.

The three groups (ADHD-I, ADHD-C, and TD) were matched in terms of age, sex, and IQ score ($P > 0.05$). One-way ANOVA was used to analyze the ADHD-RS IV scores of ADHD-I, ADHD-C, and TD groups. In the subscales of ADHD-RS IV, there were significant differences among the three groups ($P < 0.05$), and the subscale scores of the two ADHD-subtype groups were significantly higher than those of the TD group (Table 1b).

Comparison of the Asymmetry of the SN Between ADHD and TD Groups

The subcortical volume in the caudate, hippocampus, and accumbens was more leftward in the ADHD group compared with that in the TD group, and more rightward in the putamen. However, significant differences were not detected in the AIs for the SN volume between ADHD and TD groups ($P > 0.05$) (Table 2).

Table 1 Demographic and Clinical Characteristics

(a) Characteristic	ADHD n=31	TD n=31	t/χ^2	P
Age	11.67 (1.82)	11.76 (1.82)	0.201	0.841
Sex (boy/girl)	29/2	24/7	2.080	0.149
IQ	106.00 (14.29)	109.35 (15.32)	0.892	0.376
ADHD-RS IV				
Inattention	28.29 (3.24)	15.35 (4.41)	-13.168	0.000*
Hyperactivity/Impulsivity	21.61 (6.01)	13.307 (3.96)	-6.610	0.000*

(b) Characteristic	ADHD-I n=20	ADHD-C n=11	TD n=31	F/χ^2	P
Age	12.00 (1.71)	11.07 (1.93)	11.76 (1.82)	0.976	0.383
Sex (boy/girl)	18/2	11/0	24/7	3.205	0.187
IQ	103.20 (13.78)	111.09 (14.40)	109.35 (15.32)	1.430	0.248
ADHD-RS IV					
Inattention	27.85 (2.32)	29.09 (4.48)	15.35 (4.41)	86.664	0.000*
Hyperactivity/Impulsivity	18.45 (4.73)	27.36 (3.11)	13.307 (3.96)	50.483	0.000*

Notes: Continuous variables were expressed as the mean (standard deviation). *Significant at $P \leq 0.05$.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; ADHD-I, inattentive attention-deficit/hyperactivity disorder; ADHD-C, combined attention-deficit/hyperactivity disorder; IQ, intelligence quotient; ADHD-RS IV, ADHD Rating Scale IV.

Comparison of the Cortical Regions and SN Asymmetry Between the Two Subtypes in ADHD and TD Groups

The average cortical thickness AIs of 34 pairs of cortical regions extracted from the Desikan–Kiliany Atlas were compared between the two subtypes in ADHD and TD groups. There were significant differences in the cortical thickness AIs of the medial orbitofrontal, paracentral, and pars triangularis among the three groups ($P < 0.05$) (Table 3). In the pairwise comparisons, there was a significant difference between ADHD-I and TD groups in the cortical thickness AI of the medial orbitofrontal (adjusted $P = 0.003$). Moreover, the cortical thickness AI of the paracentral was significantly different between ADHD-C and TD groups (adjusted $P = 0.029$) (Table 4). However, the cortical-thickness asymmetry of the pars triangularis showed no significant difference in the pairwise comparisons. There were no significant differences in the cortical-thickness asymmetry of these three regions between the two subtypes in ADHD (adjusted $P > 0.05$).

Table 2 The SN Volume AIs Between ADHD and TD Groups

Region	AI		Z	P
SN (mm^3)	ADHD	TD		
Thalamus	−1.40 (1.74)	−1.86 (0.34)	0.824	0.410
Caudate	−2.00 (2.30)	−1.52 (0.47)	−0.993	0.321
Putamen	1.78 (2.19)	1.68 (0.29)	0.303	0.762
Pallidum	4.66 (2.99)	5.12 (0.62)	−0.246	0.805
Hippocampus	−1.94 (2.78)	−0.96 (0.45)	−1.232	0.218
Amygdala	0.28 (4.45)	1.09 (0.81)	−0.697	0.486
Accumbens	−3.76 (5.32)	−2.70 (1.08)	−0.641	0.522

Note: Continuous variables were expressed as mean (SEM).
Abbreviations: SN, subcortical nucleus; AI, asymmetry index; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing.

Results for comparisons of the cortical gray-matter volume and SN volume AIs between the two subtypes in ADHD and TD groups are summarized in Table 5. The cortical gray-matter volume AIs of the caudal anterior cingulate, isthmus cingulate, and superior frontal were significantly different among the three groups ($P < 0.05$). The SN volume AIs did not reveal significant changes between the two subtypes in ADHD and TD groups ($P > 0.05$). In the pairwise comparisons, there were significant differences in the cortical gray-matter volume AIs of the caudal anterior cingulate, isthmus cingulate, and superior frontal regions between ADHD-C and ADHD-I groups (adjusted $P = 0.050$, 0.036, and 0.045, respectively). For the comparison between ADHD-C and TD groups, the cortical gray-matter volume

Table 3 The Cortical Thickness AIs Between the Two Subtypes in ADHD and TD Groups

Region	AI			χ^2	*P*
	ADHD		TD		
Cortical regions (mm)	**ADHD-I**	**ADHD-C**			
Bankssts	−2.77 (0.68)	−0.79 (0.98)	−2.12 (0.52)	2.862	0.239
Caudal anterior cingulate	3.74 (1.05)	3.89 (1.58)	1.80 (0.79)	2.125	0.346
Caudal middle frontal	1.41 (0.47)	−0.42 (0.58)	0.89 (0.39)	5.623	0.060
Cuneus	−0.18 (0.65)	−1.20 (0.90)	−1.02 (0.54)	1.634	0.442
Entorhinal	−3.37 (1.43)	−1.25 (0.95)	−2.02 (0.88)	2.272	0.321
Fusiform	−0.62 (0.35)	−0.61 (0.36)	0.04 (0.37)	1.186	0.553
Inferior parietal	−0.60 (0.23)	−0.48 (0.41)	−0.45 (0.27)	0.476	0.788
Inferior temporal	−1.07 (0.46)	−0.32 (0.47)	−1.78 (0.40)	3.303	0.192
Isthmus cingulate	1.52 (0.66)	1.81 (1.10)	1.17 (0.76)	0.084	0.959
Lateral occipital	−1.77 (0.51)	−2.08 (0.70)	−1.88 (0.38)	0.176	0.916
Lateral orbitofrontal	1.95 (0.47)	2.32 (0.69)	1.51 (0.39)	2.132	0.344
Lingual	−0.53 (0.37)	−0.75 (0.55)	−0.71 (0.38)	0.036	0.982
Medial orbitofrontal	3.16 (0.53)	2.54 (0.60)	0.61 (0.48)	12.245	0.002*
Middle temporal	−0.49 (0.38)	−0.98 (0.63)	−0.05 (0.49)	0.276	0.871
Parahippocampal	0.73 (0.59)	0.05 (1.14)	−0.14 (0.84)	0.263	0.877
Paracentral	0.34 (0.54)	−0.66 (0.58)	1.53 (0.43)	7.269	0.026*
Pars opercularis	−0.70 (0.51)	−0.36 (0.97)	−0.35 (0.39)	0.278	0.870
Pars orbitalis	0.82 (0.70)	−1.07 (1.27)	1.75 (0.75)	5.174	0.075
Pars triangularis	−0.06 (0.50)	−1.22 (0.94)	1.19 (0.47)	6.510	0.039*
Pericalcarine	−0.58 (0.73)	0.93 (0.85)	−1.35 (0.73)	2.768	0.251
Postcentral	0.32 (0.62)	0.81 (0.87)	−0.01 (0.38)	1.890	0.389
Posterior cingulate	3.10 (0.61)	1.82 (0.72)	3.78 (0.54)	4.365	0.113
Precentral	0.86 (0.46)	0.84 (0.43)	0.63 (0.39)	1.349	0.509
Precuneus	1.08 (0.36)	0.12 (0.43)	0.71 (0.39)	3.128	0.209
Rostral anterior cingulate	2.96 (1.11)	2.70 (0.90)	2.80 (0.73)	0.075	0.963
Rostral middle frontal	1.52 (0.41)	0.84 (0.43)	1.11 (0.27)	1.250	0.535
Superior frontal	2.09 (0.33)	1.51 (0.44)	1.78 (0.26)	3.467	0.177
Superior parietal	−0.77 (0.47)	0.51 (0.68)	0.18 (0.26)	5.011	0.082
Superior temporal	−0.63 (0.40)	−0.77 (0.57)	0.08 (0.39)	5.541	0.063
Supramarginal	−0.20 (0.53)	−0.59 (0.50)	0.11 (0.42)	0.478	0.788
Frontal pole	2.57 (0.95)	1.87 (1.83)	0.87 (0.87)	1.175	0.556
Temporal pole	−2.30 (1.08)	−0.25 (1.37)	−0.88 (0.63)	1.402	0.496
Transverse temporal	0.13 (1.10)	−0.09 (0.86)	−0.34 (0.78)	0.262	0.877
Insula	0.12 (0.40)	−1.10 (0.63)	0.36 (0.37)	4.443	0.108

Notes: Continuous variables were expressed as mean (SEM). *Significant at $P \leq 0.05$.
Abbreviations: AI, asymmetry index; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; ADHD-I, inattentive attention-deficit/hyperactivity disorder; ADHD-C, combined attention-deficit/hyperactivity disorder.

Table 4 Pairwise Comparisons of the Cortical Thickness AIs Between the Two Subtypes in ADHD and TD Groups

Cortical regions (mm)	ADHD-I vs TD	ADHD-C vs TD	ADHD-C vs ADHD-I
	adjusted *P*	adjusted *P*	adjusted *P*
Medial orbitofrontal	0.003*	0.119	1.000
Paracentral	0.359	0.029*	0.659
Pars triangularis	0.238	0.062	1.000

Notes: Bonferroni correction was used in pairwise comparisons. *Significant at $P \leq 0.05$.
Abbreviations: AI, asymmetry index; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; ADHD-I, inattentive attention-deficit/hyperactivity disorder; ADHD-C, combined attention-deficit/hyperactivity disorder.

Table 5 The Cortical Gray-Matter Volume and SN Volume AIs Between the Two Subtypes in ADHD and TD Groups

Region	AI			χ^2	*P*
	ADHD		TD		
Cortical regions (mm^3)	**ADHD-I**	**ADHD-C**			
Bankssts	4.36 (2.23)	0.43 (3.05)	0.38 (1.77)	1.322	0.516
Caudal anterior cingulate	−9.35 (2.69)	4.42 (4.70)	−7.61 (2.60)	6.390	0.041*
Caudal middle frontal	6.02 (2.15)	6.72 (2.59)	7.68 (1.70)	0.137	0.934
Cuneus	−4.74 (1.41)	−6.68 (2.30)	−2.35 (1.86)	1.783	0.410
Entorhinal	2.26 (2.49)	10.13 (2.48)	3.22 (2.12)	4.760	0.093
Fusiform	1.75 (1.51)	0.38 (1.34)	1.52 (1.04)	0.615	0.735
Inferior parietal	−8.90 (1.19)	−9.15 (1.27)	−9.75 (0.95)	0.213	0.899
Inferior temporal	−0.91 (1.51)	2.41 (2.34)	0.96 (1.23)	2.777	0.249
Isthmus cingulate	3.71 (1.31)	9.97 (1.56)	3.86 (1.29)	7.616	0.022*
Lateral occipital	−1.53 (1.12)	−2.24 (2.11)	−0.05 (0.99)	1.771	0.412
Lateral orbitofrontal	2.87 (0.84)	1.51 (1.18)	1.93 (0.69)	0.501	0.779
Lingual	−0.73 (1.11)	−1.76 (0.83)	−2.44 (0.86)	1.419	0.492
Medial orbitofrontal	−0.12 (1.55)	−2.06 (1.52)	−1.59 (1.02)	0.352	0.839
Middle temporal	−5.40 (1.29)	−4.30 (1.88)	−2.98 (0.92)	2.267	0.322
Parahippocampal	1.46 (1.28)	3.37 (2.10)	2.50 (1.54)	1.044	0.593
Paracentral	−5.22 (2.03)	−9.00 (2.04)	−3.79 (1.43)	3.874	0.144
Pars opercularis	7.97 (1.88)	10.57 (2.14)	8.88 (1.90)	1.076	0.584
Pars orbitalis	−11.49 (1.70)	−13.20 (1.61)	−8.66 (1.25)	4.126	0.127
Pars triangularis	−7.15 (1.75)	−10.88 (2.11)	−7.99 (1.59)	1.616	0.446
Pericalcarine	−4.73 (1.17)	−8.45 (1.25)	−7.48 (1.51)	5.137	0.077
Postcentral	1.66 (1.47)	2.86 (1.41)	3.65 (1.27)	1.438	0.487
Posterior cingulate	2.00 (2.17)	5.51 (2.30)	0.64 (1.42)	4.066	0.131
Precentral	0.41 (1.11)	1.61 (1.38)	−0.26 (0.69)	2.099	0.350
Precuneus	−0.28 (1.25)	−1.88 (1.31)	−0.43 (0.98)	1.187	0.552
Rostral anterior cingulate	9.91 (2.39)	15.38 (4.77)	12.31 (2.27)	1.197	0.550
Rostral middle frontal	2.22 (1.30)	−1.77 (0.87)	−1.22 (0.64)	3.079	0.215
Superior frontal	3.61 (0.89)	0.39 (0.91)	2.32 (0.59)	6.000	0.050*
Superior parietal	−0.08 (1.31)	1.86 (1.67)	0.63 (0.83)	2.465	0.292
Superior temporal	1.90 (1.03)	2.36 (1.20)	3.09 (0.79)	0.231	0.891
Supramarginal	5.37 (1.39)	3.31 (1.84)	4.16 (1.21)	1.113	0.573
Frontal pole	−11.72 (2.18)	−15.39 (3.50)	−14.05 (1.46)	2.413	0.299
Temporal pole	3.86 (1.84)	7.86 (2.56)	4.32 (1.33)	1.326	0.515
Transverse temporal	14.76 (1.45)	18.00 (2.29)	14.93 (1.30)	1.913	0.384
Insula	−1.32 (0.98)	−0.61 (0.54)	−0.28 (0.81)	0.753	0.686
SN (mm^3)					
Thalamus	−1.03 (0.37)	−2.08 (0.53)	−1.86 (0.34)	3.537	0.171
Caudate	−1.89 (0.53)	−2.20 (0.67)	−1.52 (0.47)	1.076	0.584
Putamen	1.50 (0.48)	2.29 (0.70)	1.68 (0.29)	1.212	0.546
Pallidum	3.92 (0.72)	6.00 (0.61)	5.12 (0.62)	3.623	0.163
Hippocampus	−1.66 (0.59)	−2.45 (0.92)	−0.96 (0.45)	2.062	0.357
Amygdala	0.20 (1.07)	0.42 (1.19)	1.09 (0.81)	0.487	0.784
Accumbens	−3.28 (1.27)	−4.64 (1.43)	−2.70 (1.08)	1.224	0.542

Notes: Continuous variables were expressed as mean (SEM). *Significant at $P \leq 0.05$.

Abbreviations: SN, subcortical nucleus; AI, asymmetry index; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; ADHD-I, inattentive attention-deficit/hyperactivity disorder; ADHD-C, combined attention-deficit/hyperactivity disorder.

AI of the isthmus cingulate was significantly different (adjusted $P = 0.032$). There were no significant differences in the asymmetry of cortical gray-matter volume in the caudal anterior cingulate, isthmus cingulate, or superior frontal regions between ADHD-I and TD groups (adjusted $P > 0.05$ for all) (Table 6).

Table 6 Pairwise Comparisons of the Cortical Gray-Matter Volume AIs Between the Two Subtypes in ADHD and TD Groups

Cortical regions (mm^3)	ADHD-I vs TD	ADHD-C vs TD	ADHD-C vs ADHD-I
	adjusted *P*	adjusted *P*	adjusted *P*
Caudal anterior cingulate	1.000	0.076	0.050*
Isthmus cingulate	1.000	0.032*	0.036*
Superior frontal	0.520	0.407	0.045*

Notes: Bonferroni correction was used in pairwise comparisons. *Significant at $P \leq 0.05$.
Abbreviations: AI, asymmetry index; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; ADHD-I, inattentive attention-deficit/hyperactivity disorder; ADHD-C, combined attention-deficit/hyperactivity disorder.

Correlation Between the AIs of Cortical Regions and the Severity of ADHD Symptoms

The cortical thickness AI of the medial orbitofrontal region was significantly positively correlated with ADHD symptoms (inattention) (r = 0.394, $P = 0.002$) (Figure 1). Even so, a significantly negative correlation was revealed between the cortical thickness AI of the paracentral and ADHD symptoms (inattention) (r = −0.296, $P = 0.019$) (Figure 2). Besides, the increased severity of ADHD symptoms on the hyperactivity/impulsivity subscale was associated with a significantly increased cortical gray-matter volume AI in the isthmus cingulate (r = 0.283, $P = 0.026$) (Figure 3).

Discussion

We investigated the changes in the asymmetry of cortical and subcortical structures between children and adolescents with ADHD and TD individuals. Moreover, this study was the first to explore differences in cortical and subcortical asymmetry between different subtypes of ADHD and TD participants. Although asymmetry in the SN in ADHD group did not reveal significant differences (as we hypothesized), specific cortical regions showed differences in different subtypes of ADHD. In the present study, compared with TD individuals, different subtypes of ADHD demonstrated altered cortical asymmetry in the medial orbitofrontal, paracentral, pars triangularis, caudal anterior cingulate, isthmus cingulate, and superior frontal

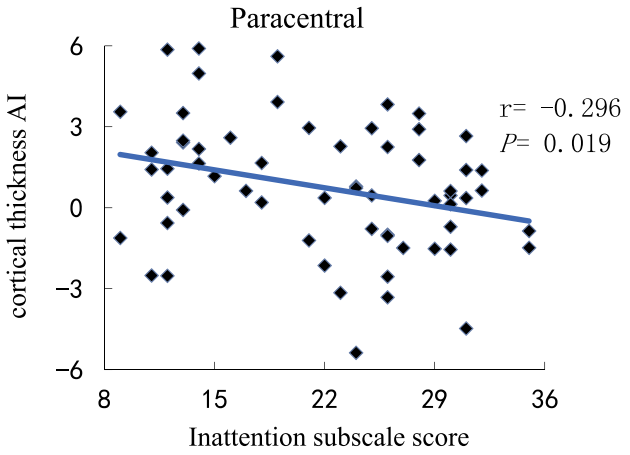

Figure 2 Correlation between the cortical thickness AI in the paracentral and the severity of ADHD symptoms on the inattention subscale score.

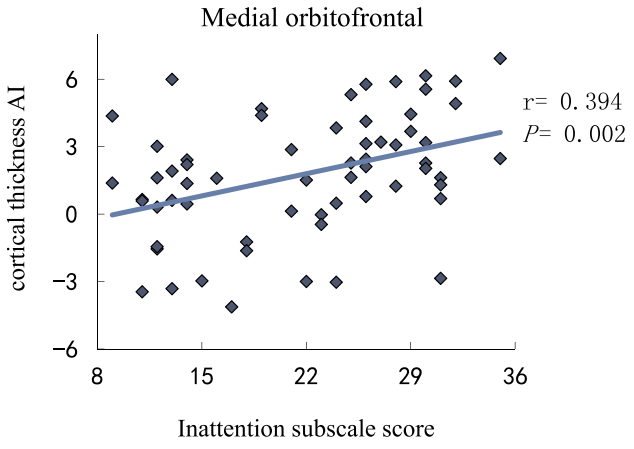

Figure 1 Correlation between the cortical thickness AI in the medial orbitofrontal and the severity of ADHD symptoms on the inattention subscale score.

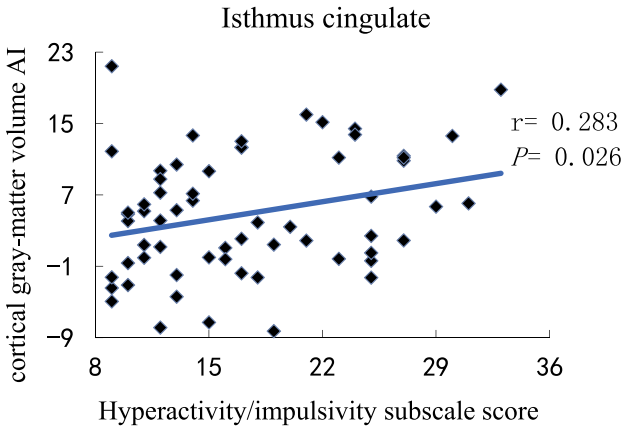

Figure 3 Correlation between the cortical gray-matter volume AI in the isthmus cingulate and the severity of ADHD symptoms on the hyperactivity/impulsivity subscale score.

regions. These regions are parts of the orbitofrontal and cingulate circuits. Patients with impaired orbitofrontal and cingulate circuits can reveal automatic deficits and personality abnormalities, including behavioral disinhibition, emotional instability, and reduced motivation.[29,30] These localized structural changes provide strong evidence that ADHD might have multiple deficits in the neural networks in the brain. The specific mechanism of cortical structural alterations is incompletely understood. A cadaver study by Chaudhry and coworkers supported the possibility that a reduced thickness in the pyramidal layer in the frontal lobe could elicit decreased cortex thickness.[20] Pyramidal neurons are important components of the cortex, and their functions are closely related to advanced cognitive functions. Any alteration in these neurons might cause abnormal connections between and within the gyrus, leading to the clinical symptoms of ADHD.

The fronto-cortical and fronto-subcortical circuits are associated with controlled and automatic deficits.[30,31] These functions could be impaired in children and adolescents with ADHD. The orbitofrontal cortex is connected to the frontal control system (eg, dorsolateral prefrontal cortex) and the limbic system (eg, cingulate and nucleus accumbens).[32,33] The right medial orbitofrontal cortical gray-matter volume was increased in treatment-naive ADHD, whereas the cortical gray-matter volume comprises the cortical surface area and cortical thickness.[24] An increased cortical gray-matter volume is accompanied by thinning of cortical thickness. These phenomena were consistent with the asymmetry in the cortical thickness of the orbitofrontal cortex measured between ADHD-I and TD groups in our study. Furthermore, a recent study showed that the ADHD-I group is slower than the TD group in terms of automatic processing speed.[2] Combined with our results, the cortical abnormalities of the orbitofrontal cortex in the ADHD-I group might be related to automatic deficits. The structural abnormality in the orbitofrontal cortex might be a pathophysiological basis for the connectivity of the cortical-limbic system in ADHD. The paracentral lobule is located on the medial side of the frontal-parietal lobe and manages movement and sensation. In our study, the cortical asymmetry in the paracentral region was significantly different between ADHD-C and TD groups. Moreover, an increased inattention symptom score was correlated with decreased cortical thickness AI. A study by Zou and colleagues based on the variability of the resting-state fMRI signal showed increased right-lateralization in the paracentral lobule of ADHD patients, whereas there was no difference between the ADHD-C and ADHD-I groups in this region.[34]

Impulsive aggression is observed widely in children with ADHD, and is linked to the unsatisfied expectation of a reward.[33] Studies have shown that impulsive aggression is characterized by severe structural changes in the amygdala, anterior cingulate cortex, and orbitofrontal cortex.[33,35–37] As we have shown, the asymmetry in the cortical gray-matter volume in the isthmus cingulate was correlated with the hyperactivity/impulsivity score. However, a multivariate-analysis study demonstrated that the white-matter fibers of connectivity in the fronto-accumbal circuit and cortical thickness within the orbitofrontal cortex mainly explained aggression, but not impulsivity, in treatment-naive children with ADHD.[33] Those results were partially in accordance with our findings, and revealed that the cortical-thickness asymmetry in the medial orbitofrontal was associated with the inattention symptom score, but not the hyperactivity/impulsivity symptom score. The isthmus cingulate connects the cingulate gyrus to the parahippocampal gyrus (the function of which is controversial and might be related to verbal ability and adaptability) and pars triangularis which, as a part of Broca's area, plays a vital part in the processing of language and interpersonal information.[38] In our study, participants with ADHD had asymmetry abnormalities in these two cortical regions compared with those in TD individuals. These abnormalities in the asymmetry of cortical structures might be a specific cue for verbal and interpersonal processing in children and adolescents with ADHD. The superior frontal region is primarily responsible for self-awareness, rational decision-making, and motor function. Our study demonstrated that ADHD had cortical-volume asymmetry in this region. A graph-theory approach has revealed that the dorsal superior frontal gyrus, central sulcus, and putamen in adults with ADHD have reduced nodal efficiency asymmetry.[39] Also, we found alterations in cortical-volume asymmetry in the caudal anterior cingulate, isthmus cingulate, and superior frontal regions between ADHD-I and ADHD-C groups. The difference between the two subtypes of ADHD patients is that ADHD-C patients have mixed hyperactivity/impulsivity symptoms. Our results suggest that the asymmetry of cortical gray-matter volume in the frontal and cingulate cortex might be the specific alterations between individuals with ADHD-I and ADHD-C subtypes.

Limitations

Our study had three main limitations. First, the study cohort was very small, so this study could be considered to be a pilot study. We must interpret with caution any

asymmetry abnormalities that we distinguished. More participants are needed to obtain more robust results. Second, we did not have a patient cohort with the ADHD-HI subtype, and the results would have been more comprehensive if we had included all subtypes of ADHD. Third, we did not exclude ADHD patients taking medications, and some ADHD patients might have had a history of taking medications, which may have effects on brain structure (and our results).

Conclusion

Altered cortical and subcortical morphological asymmetry in children and adolescents with ADHD were predominantly located in cortical orbitofrontal and cingulate circuits. There were differences between patients with ADHD-I and ADHD-C subtypes in terms of the asymmetry of cortical regions in the cingulate and frontal cortex. These abnormalities were associated (at least in part) with the severity of ADHD symptoms. Hence, brain asymmetry could be an appropriate precursor of morphological alterations in neurodevelopmental disorders. These findings may provide potential monitoring for the valid diagnosis and treatment of ADHD.

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Disclosure

The authors report no conflicts of interest in this work.

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