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Changes of Brain Structure and Function in ADHD Children

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Abstract To explore the changes of brain structure and function in attention-deficit/hyperactivity disorder (ADHD), fifteen ADHD patients (inattention subtype) and 15 normal control participants were recruited, the brain structure and function of these subjects were investigated by combining structural magnetic resonance imaging (MRI), diffusion tensor imaging and resting-state functional MRI. The results showed that ADHD patients had a significant decrease in the volume of the white matter ($P = 0.04$), and a trend toward decreased volume of brain structures except for the putamen and globus pallidus. The visualization of statistical difference maps of the cortical thickness showed that ADHD patients had focal thinning in bilateral frontal regions and the right cingulate cortex ($P < 0.05$ uncorrected, except for a cluster threshold of 10 voxels). Statistical analysis of the FA maps revealed that ADHD patients had significantly decreased FA in the forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia ($P < 0.05$ uncorrected as above). ADHD patients had significantly decreased functional connectivity in the anterior cingulate cortex, posterior cingulate cortex, lateral prefrontal cortex, left precuneus and thalamus, but increased functional connectivity in bilateral posterior medial frontal cortex in the default mode network ($P < 0.05$ uncorrected as above). Our results provide new insights into the changes of the brain structure and function in ADHD, which suggests that alterations in the brain structural and functional connectivity might implicate the pathophysiology of ADHD.

Keywords Resting-fMRI · Functional connectivity · Attention-deficit/hyperactivity disorder · Default mode network

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders and can continue through adolescence and adulthood. The symptoms of ADHD include difficulty in staying focused, paying attention, controlling behavior, and hyperactivity (Garrett et al. 2008; Krain and Castellanos 2006). Previous studies showed that the anatomical abnormalities associated with ADHD can be visualized using high-resolution magnetic resonance imaging (MRI) (Berquin et al. 1998; Castellanos et al. 1996; Mataro et al. 1997). However, there are important discrepancies among various studies, probably due to very small sample sizes or the use of different techniques (Table 1), and these MR studies could not identify microstructural properties of white matter. Diffusion tensor imaging (DTI) is a valuable tool in studying the microstructure of the brain in vivo, and has the ability to reveal microstructural properties of white matter (Silk et al. 2008). Therefore, among the in vivo MR imaging techniques, DTI in particular is a useful tool for examining white matter integrity in ADHD (Ashtari et al. 2005; Makris et al. 2008a; Pavuluri et al. 2009).

Table 1 Summary of structural and functional MRI studies in ADHD

Study	Subjects	Method	Principal Findings in ADHD
Castellanos et al. (2002)	152 ADHD patients (age: 5–18 years), 139 controls (age: 4.5–19 years)	Structural MRI	Smaller gray matter and white matter volumes in unmed vs. med or controls in all subdivided areas of the brain. Initial caudate nucleus difference (ADHD vs. NC) disappear over adolescence
Mostofsky et al. (2002)	12 ADHD males (age: 8–14 years), 12 control males (age: 8–14 years)	Structural MRI	Smaller white matter and gray matter volumes than in NC. Left white matter and right gray matter smaller than in NC.
Carmona et al. (2005)	25 ADHD patients (age: 11.63 ± 2.04 years), 25 healthy volunteers (age: 11.18 ± 3.21 years)	Structural MRI	ADHD brains volume decrease of 5.4% compared to controls. Regionally specific effects in the left fronto-parietal areas, left cingulate cortex, parietal lobe, temporal cortices and the cerebellum. No differences in white matter volume.
Garrett et al. (2008)	24 ADHD patients (age: 15–19 years) and 10 controls (age: 15.4–18.3 years) and 12 archived controls (age: 14.1–18.8 years).	Structural MRI	Cerebral total tissue was similar between groups. The right caudate and right inferior frontal lobe volumes larger in ADHD than in NC. Increasing left caudate volume in ADHD patients associated with decreasing functional activation of this region.
Wolosin et al. (2009)	21 ADHD patients (age: 8.7–12.8 years), 35 controls (age: 8.4–13.0 years).	Structural MRI	ADHD patients showed a decrease in total cerebral volume and total cortical volume of over 7% and 8%. No significant differences in cortical thickness.
Ashtari et al. (2005)	18 ADHD patients (age: 8.94 ± 1.5 years), 15 volunteers (age: 9.13 ± 1.4 years)	DTI	ADHD patients had decreased FA in right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas.
Hamilton et al. (2008)	17 children and adolescents with ADHD, 16 controls.	DTI	ADHD patients had significantly lower FA in the corticospinal tract and the superior longitudinal fasciculus compared with controls
Silk et al. (2008)	15 ADHD males (age: 8–18 years), 15 healthy males (age: 8–18 years).	DTI	ADHD patients showed greater FA in white-matter regions underlying inferior parietal, occipito-parietal, inferior frontal, and inferior temporal cortex.
Zang et al. (2007)	13 ADHD boys (age: 13.0 ± 1.4 years), 13 matched controls (age: 13.1 ± 0.6 years).	Resting fMRI	ADHD patients had decreased ALFF in the right inferior frontal cortex, left sensorimotor cortex, and bilateral cerebellum and the vermis, but increased ALFF in the right anterior cingulated cortex, left sensorimotor cortex, and bilateral brainstem.
Tian et al. (2008)	12 ADHD patients (age: 11–14.8 years), 12 controls (age: 12.5–14.1 years)	Resting fMRI	ADHD patients exhibited more significant resting-state activities in basic sensory and sensory-related cortices.
Uddin et al. (2008)	20 ADHD patients (age: 34.9 ± 9.9 years), 20 comparison subjects (age: 31.2 ± 9.0 years).	Resting fMRI	Reduced network homogeneity within the default mode network in ADHD subjects compared to age-matched controls, particularly between the precuneus and other default mode network regions.
Castellanos et al. (2008)	20 ADHD patients and 20 age- and sex-matched healthy volunteers.	Resting fMRI	ADHD patients showed decreases in the functional connectivity between the anterior cingulate and precuneus/posterior cingulate cortex regions, and also in connectivity between precuneus and other default-mode network components, including ventromedial prefrontal cortex and portions of posterior cingulate.

Blood oxygenation level-dependent (BOLD) fMRI is also a valuable technique for ADHD pathology analysis (Hale et al. 2007; Roy et al. 2009; Rubia 2002; Solanto et al. 2009; Suskauer et al. 2008; Tian et al. 2008). Up to the present time, almost all former BOLD fMRI studies on ADHD are task-based (Makris et al. 2008a). As compared to the task-based fMRI studies, studies conducted during resting state are easy to carry out (without experiment design and subject training) and the results are comparable across different patient groups (Greicius and Menon 2004; Greicius et al. 2009; Long et al. 2008; Raichle et al. 2001; Thomason et al. 2008). Recently, resting state has been applied to the pathology analyses of neuropsychiatric disorders such as depression, Alzheimer's disease and multiple sclerosis (Greicius et al. 2007; He et al. 2007; Lowe et al. 2008). The most prominent network in the clinical neuroscience literature on spontaneous intrinsic brain activity is the default mode network (DMN). The DMN comprises medial (medial prefrontal cortex, posterior cingulate/precuneus) and lateral (posterior parietal) brain regions that routinely exhibit coherent decreases in activity during attention-demanding cognitive tasks (Greicius et al. 2003, 2007; Raichle et al. 2001). Tian et al. (2008) found that the ADHD patients exhibited more significant resting-state brain activities in basic sensory and sensory-related cortices, and that dACC had more significant resting-state functional connectivity with several other brain regions in the ADHD patients as compared to the controls (Tian et al. 2006). However, other studies found reduced functional connectivity between the anterior cingulate cortex and various nodes of the DMN (Castellanos et al. 2008; Uddin et al. 2008). In a recent review, DMN interference during task performance was suggested to be a potential underlying cause of performance variability in ADHD (Sonuga-Barke and Castellanos 2007). Although there are numerous theoretical reasons for suspecting DMN dysfunction in ADHD, the findings of the previous studies in ADHD are variable and their interpretations regarding the functional abnormalities are controversial (Table 1). If a more detailed examination of DMN integrity in ADHD is warranted, a study carried out during resting state will probably provide us a new perspective on ADHD pathology.

The aim of the study is to investigate the changes of brain structure and function in ADHD patients by combining high resolution structural MRI with diffusion tensor imaging, and to explore the differences of the resting-state default mode network between ADHD patients and normal control subjects by resting fMRI. We hypothesize that there are structural changes in the white matter integrity and gray matter, and abnormal default mode network in the ADHD patients when compared to the normal control subjects.

Methods

Subjects

Fifteen ADHD patients (age range 10.6–14.8 years, mean 12.65 ± 1.82 years) and 15 normal control participants (age range 10.5–15.0 years, mean 13.21 ± 1.73 years) were recruited. Inclusion criteria for all subjects were within the age range of 10–15 years, male, right-handedness, and IQ >80 (as assessed with Wechsler Intelligence Scale for Children-revised (WISC-R)). Exclusion criteria for all subjects were any contraindications for MRI and neuropsychiatric disorder such as childhood schizophrenia, mental retardation and epilepsy. Group matching was based on age, gender, and education. All the fifteen ADHD patients met the DSM-IV criteria for ADHD (as assessed with Clinical Diagnostic Interview Scale, CDIS). All of ADHD patients were of the inattention subtype, and medication-free for at least half a year. The parents of all participants gave written informed consent after receiving a complete description of the study.

Image Acquisition

The resting-state fMRI data were acquired by a Siemens 3T scanner using the following parameters: TR/TE/FA = 2000 ms/30 ms/90°, 30 slices, thickness = 4.0 mm, FOV = 220 mm × 220 mm. Each session lasted for 320 s. During the resting state, the subjects were told not to concentrate on any particular subject, but just to relax with their eyes closed. Then 12 direction diffusion tensor images were acquired with a spin-echo echo-planar imaging pulse sequence on each subject for six times on average (b = 1000 s/mm^2, matrix = 128 × 128, 34 axial 2.5 mm slices with zero gap, TR/TE/FA = 6500 ms/90 ms/90°). High-resolution T1-weighted images were also acquired with 3D MPRAGE sequence (TR/TE/FA = 2600 ms/3.93 ms/8°, matrix = 256 × 240, with 1 mm slice thickness).

Image Processing and Analysis

The volume of brain structures and the cortical thickness were analyzed by Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Automated surface reconstruction yielded measurements of the cortical thickness for each subject's entire brain and computed cross-subject statistics based on the cortical anatomy. Statistical analysis of the volume of brain structures was analyzed by SPSS13.0. Statistical thickness difference maps were generated by performing t-tests between ADHD patients and normal control subjects, significance was placed at $P < 0.05$, uncorrected for

multiple comparisons, except for a cluster extent threshold of 10 voxels.

Post-processing of the DTI data included eddy current correction and the computations of the diffusion tensor elements. Then FA maps were generated in FSL (www.fmrib.ox.ac.uk/fsl), on which the white matter integrity was investigated using the SPM5 package (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The non-diffusion-weighted (b0) images were normalized to the Montreal Neurological Institute (MNI) EPI template that is supplied by the SPM5 package. The FA maps were then spatially transformed according to the normalized b0 images. Normalized images were re-formatted into 69 slices with $2 \times 2 \times 2$ mm^3 voxels. The FA maps were smoothed with Gaussian kernels with full width half maximum (FWHM) of 6 mm. An intergroup two-sample t-test comparison was performed using an absolute threshold of FA >0.15. The contrasts used $P < 0.05$, uncorrected for multiple comparisons, except for a cluster extent threshold of 10 voxels.

The resting-state fMRI data were spatially normalized to the standard MNI (Montreal Neurological Institute) template and resampled to 3 mm $\times$ 3 mm $\times$ 3 mm. Subsequently, the functional scans were spatially smoothed with a 4 mm $\times$ 4 mm $\times$ 4 mm full width half maximum Gaussian kernel to decrease spatial noise. All these processes were also conducted using SPM5. For each subject, the smoothed, normalized fMRI images were concatenated across time to form a single four-dimensional image. This image was then analyzed with FSL's melodic ICA software (www.fmrib.ox.ac.uk/fsl/melodic2). ICA is a statistical technique that separates a set of signals into independent—uncorrelated and non-Gaussian-spatiotemporal components. In order to overcome the difficulty of sorting ICA components, Greicius et al. have developed a template-matching procedure which identifies a network of interest by its goodness-of-fit to a pre-specified template mask (Greicius et al. 2007; Greicius and Menon 2004). The automated, two-step process developed in previous studies (Greicius et al. 2003, 2007; Greicius and Menon 2004) was then employed to select the components in each subject that most closely matched the default-mode network. Using SPM, two-sample t-tests were calculated to compare the default-mode network between the two groups, the best-fit components from both groups were entered into the analysis, and the z-scores (assigned by the ICA) at each voxel were averaged within each group and then compared across groups. The contrasts used $P < 0.05$, uncorrected for multiple comparisons, except for a cluster extent threshold of 10 voxels. Statistical maps were superimposed on the mean normalized high resolution T1-weighted images of all the subjects.

The two most widely used spaces in the neuroscience community are the Talairach space and the Montreal Neurological Institute (MNI) space. The International Consortium of Brain Mapping (ICBM) has adopted the ICBM152 template as an international standard, this ICBM152 template is used by several functional imaging analysis packages, such as SPM5 and FSL. The Talairach space is based on a stereotaxic atlas of the human brain published by Talairach and Tournoux, this template is used by FREESURFER software. The Talairach coordinate system has become the standard reference for reporting the brain locations. For reporting the brain locations in a common reference space, we obtained the Talairach coordinates of the center-of-gravity of focal thinning regions in FREESURFER using the Talairach space. As to SPM and FSL, we obtained the Talairach coordinates of the center-of-gravity of each cluster with the mni2tal script (http://eeg.sourceforge.net/mridoc/mri_toolbox/mni2tal.html), a tool commonly used to map the MNI coordinates to the Talairach coordinates.

Results

The volume of the white matter decreased significantly in ADHD patients compared with normal control subjects ($P = 0.04$), and the volume of the brain structures was generally smaller in ADHD patients than in control subjects except for the putamen and globus pallidus (Table 2).

Table 2 Average volume of different structures (mm^3), the *P*-values and decrease percentage between ADHD patients and NC subjects

	NC	ADHD	*P*-values	Percentage
White matter	472407 ± 67234	394527 ± 37741	0.04*	−16
Cerebral cortex	453042 ± 44651	411761 ± 47860	0.12	−9
Thalamus	13757 ± 1933	13483 ± 1588	0.75	−2
Caudate nucleus	8371 ± 1490	7719 ± 1438	0.27	−8
Putamen	11200 ± 729	11854 ± 1737	0.36	+6
Globus pallidus	3808 ± 585	3832 ± 668	0.91	+1
Hippocampus	7778 ± 913	7481 ± 1239	0.60	−4
Amydala	3770 ± 435	3670 ± 474	0.67	−3
Accumbens	1444 ± 239	1400 ± 210	0.66	−3

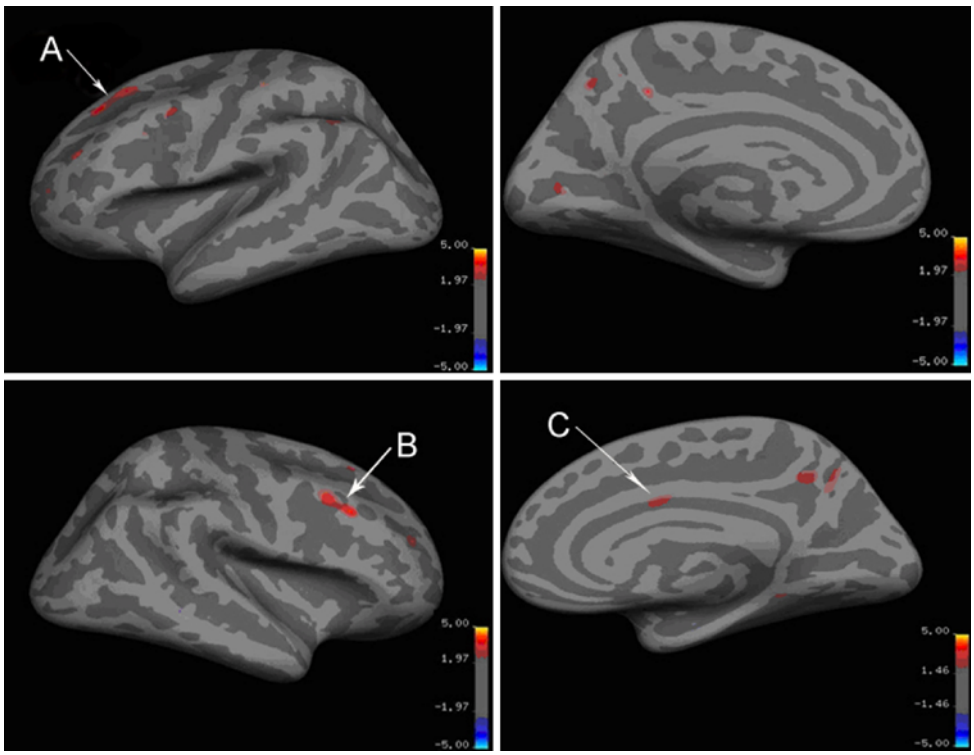

Fig. 1 Focal cortical thinning in bilateral frontal regions and the right cingulate cortex in ADHD patients. (*A*) left frontal cortex, (*B*) right frontal cortex, (*C*) right cingulate cortex. The *bar* shows the T-value

ADHD patients had a decrease of 9% in the volume of cerebral cortex and of 8% in the volume of caudate nucleus, though there is no significant difference with *P*-value 0.12 and 0.27 respectively. The visualization of statistical difference maps of the cortical thickness showed focal thinning in bilateral frontal regions and the right cingulate cortex in ADHD patients ($P < 0.05$, uncorrected) (Fig. 1; Table 3).

Statistical analysis of the FA maps revealed a significant decrease of FA in ADHD patients compared to normal controls ($P < 0.05$, uncorrected), and decreased FA was observed in the forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia in ADHD subjects (Fig. 2; Table 3).

Comparing the resting-state default mode network between ADHD patients and normal control subjects, we found the ADHD patients had significantly decreased functional connectivity in brain regions such as the anterior cingulate cortex, posterior cingulate cortex, lateral prefrontal cortex, left precuneus and thalamus, but had increased functional connectivity in brain regions such as bilateral medial frontal lobe($P < 0.05$, uncorrected) (Fig. 3; Table 3).

Discussion

The results show that ADHD children had a significant decrease in the volume of white matter ($P = 0.04$) and had a decrease of 9% in the volume of cerebral cortex and of 8% in the volume of caudate nucleus (though there is no significant difference with their *P*-values of 0.12 and 0.27 respectively), which are similar with the previous studies (Carmona et al. 2005; Castellanos et al. 1996; Wolosin et al. 2009; Ahrendts et al. 2010). On the other hand, our results show that there is no significant difference of the volume of putamen and globus pallidus between ADHD patients and control subjects (with their *P*-values of 0.36 and 0.91 respectively), which is similar with the previous study by Wellington et al. (2006). Wellington et al. (2006) reported that no differences were found in the total, left, and right putamen volumes across the ADHD patients or control group, but a significant reversal of asymmetry across groups was found: children with ADHD tended to have a smaller left putamen than right, while the control group tended to have a smaller right putamen than left.

The statistical tests of FA maps showed that ADHD patients had a significant decrease of FA in the forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia, which is similar to the previous studies (Hamilton et al. 2008; Pavuluri et al. 2009). Hamilton et al. (2008) reported that ADHD patients had significantly lower FA in the corticospinal tract and the superior longitudinal fasciculus than controls, supporting that disruptions in motor and attentional networks may contribute to ADHD pathophysiology. Rusch et al. (2007a, b, 2010) found increased mean diffusivity in inferior frontal white matter, and

Table 3 Significant clusters identified from different imaging techniques in ADHD patients compared with controls

Anatomic definition	Imaging technique	Results	Voxels	Talairach coordinates		
				X	*Y*	*Z*
Right frontal lobe	Cortical thickness	Decreased	265	38	24	26
Left frontal lobe	Cortical thickness	Decreased	203	−19	38	32
Right cingulate cortex	Cortical thickness	Decreased	128	5	−2	25
Right forceps minor	FA	Decreased	276	11	30	3
Left forceps minor	FA	Decreased	258	−12	31	3
Right internal capsule	FA	Decreased	469	20	−4	18
Left internal capsule	FA	Decreased	184	−18	−5	17
Right corona radiata	FA	Decreased	218	23	17	27
Left corona radiata	FA	Decreased	186	−23	16	27
Splenium of the corpus callosum	FA	Decreased	165	−6	−37	17
Right basal ganglia	FA	Decreased	122	24	−3	13
Left basal ganglia	FA	Decreased	108	−25	−4	13
Anterior cingulate cortex	Functional connectivity	Decreased	288	−4	42	6
Posterior cingulate cortex	Functional connectivity	Decreased	246	−2	−48	7
Left lateral prefrontal cortex	Functional connectivity	Decreased	183	−14	66	−1
Left thalamus	Functional connectivity	Decreased	106	−8	−22	4
Right posterior medial frontal cortex	Functional connectivity	Increased	154	6	29	−11
Left posterior medial frontal cortex	Functional connectivity	Increased	86	−5	29	−11

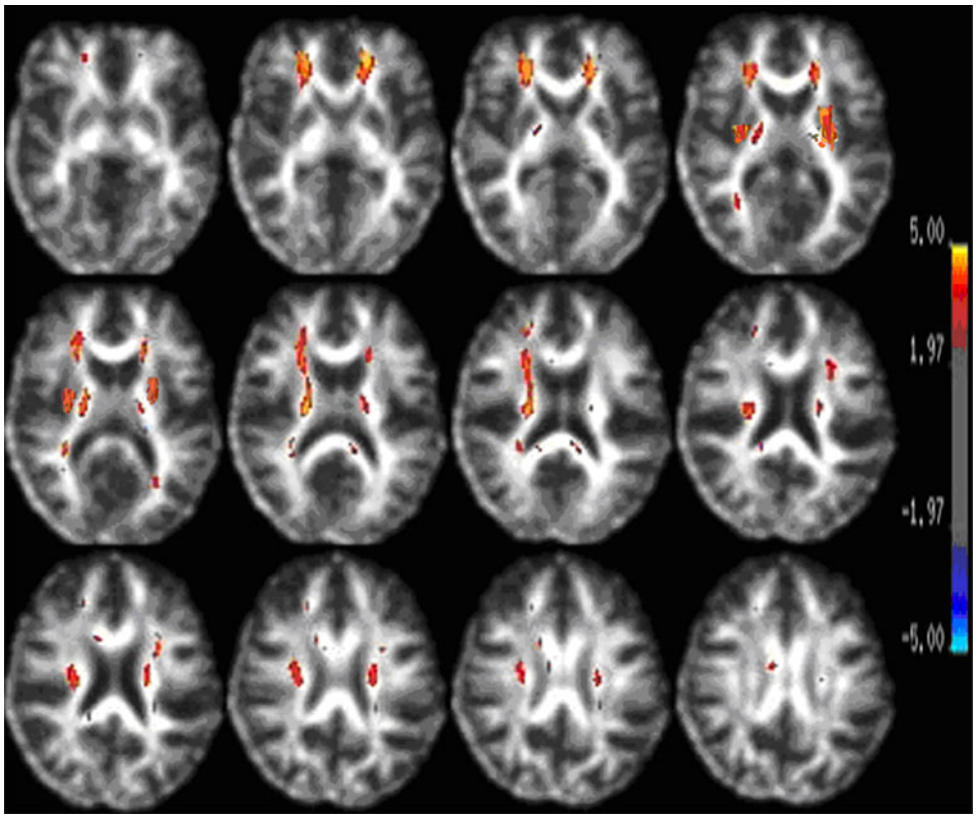

Fig. 2 ADHD patients had decreased FA in the forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia. The *bar* shows the T-value

decreased interhemispheric structural connectivity between both ACCs in fiber tracts that pass through the anterior corpus callosum and connect dorsal areas of the ACCs among women with BPD and comorbid ADHD. Pavuluri et al. (2009) also observed significantly lower FA in anterior corona radiata, anterior limb of the internal

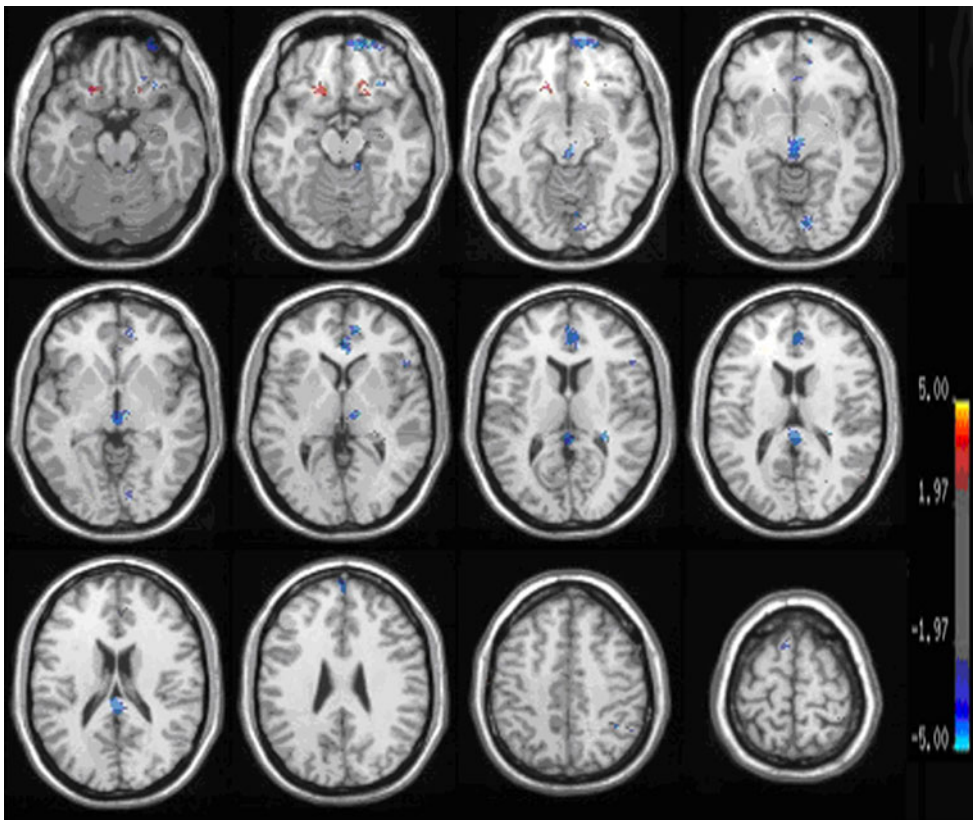

Fig. 3 ADHD patients had significantly decreased functional connectivity in the anterior cingulate cortex, posterior cingulate cortex, lateral prefrontal cortex, left precuneus and the thalamus, but increased functional connectivity in bilateral posterior medial frontal cortex. The *bar* shows the T-value

capsule, superior region of the internal capsule, posterior limb of the internal capsule, superior longitudinal fasciculus, inferior longitudinal fasciculus, cingulum, and splenium in ADHD patients than that in NC subjects. These affected fibers (the forceps minor, the internal capsule, the corona radiata) anatomically connected with the bilateral frontal regions and the cingulate cortex, which have focal thinning showing by the statistical difference maps of the cortical thickness.

The thickness of cerebral cortex is an additional indicator of integrity of cytoarchitecture in the cortex (Luders et al. 2009; Makris et al. 2007; Shaw et al. 2006). The visualization of statistical difference maps of the cortical thickness showed focal thinning in the bilateral frontal regions and the right cingulate cortex in ADHD, which is similar to some previous studies (Makris et al. 2007; Shaw et al. 2006). Makris et al. (2007) found there was a significant cortical thinning in ADHD in a distinct cortical network supporting attention especially in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal, and the anterior cingulate cortices. Shaw et al. (2006) also found that children with ADHD had global thinning of the cortex, most prominently in the medial and superior prefrontal and precentral regions; children with worse clinical outcome had a thinner left medial prefrontal cortex at baseline than the better outcome group and controls. However, Wolosin et al. (2009) found only a significant decrease in cortical folding bilaterally, but no significant differences in cortical thickness were detected. And Rusch et al. (2007) found Women with BPD and comorbid ADHD had a thinner isthmus of the corpus callosum, compared with healthy women. Our results provide new insights into the difference of the cortical thickness in ADHD, revealing the selective thinning of cerebral cortex that subserves attention and executive function. Because of some limitations, the particular thinning cortical regions identified in this study should be interpreted cautiously and subjected to replication in larger samples. An important limitation of this study is the small sample size, and another is the fully automated method used in FreeSurfer software. The technique of three-D parametric surface modeling of FreeSurfer overcomes the limitations of volumetric segmentation and represents complex sulcal structures. However, errors in the cortical surface model still exist in folded regions because of the limit of the resolution in volume images, which may occasionally obscure subtle neuroanatomic effects (Devlin and Poldrack 2007; Makris et al. 2008b). On the other hand, Cortical thickness measurements suggested differences in rather small spots in the cingulate cortex and dorsolateral frontal lobe, the termination fields of decreased FA in forceps minor, internal capsule, and corona radiata are much larger showed by DTI analysis. The mismatches between the two methods could be caused by: (1) Cortical

thickness measurements just focus on the cortex, but the difference of white matter (there are significant decrease of the volume of the white matter in ADHD patients) can't display on the statistical maps of the cortical thickness. (2) DTI just focuses on the white matter and more sensitive to the FA change of the white matter. Low FA values of the white matter may reflect axonal degeneration, and/or less well-organized tracts, and may be induced by a variety of influences. (3)These affected fibers anatomically connected with the cortical areas (bilateral frontal regions and the cingulate cortex). They can influence each other, but these changes maybe are not in a synchronous manner, and it's still unknown which is the initiator or the starter. Anyway, future studies are needed to further explore the relationships between the cortex and white matter abnormalities in this disorder.

Comparing the resting-state default mode network between ADHD and NC subjects, we found that the ADHD patients had significantly decreased functional connectivity in the anterior cingulate cortex, posterior cingulate cortex, lateral prefrontal cortex, left precuneus and thalamus, as well as significantly decreased structural connectivity in the forceps minor, and the splenium of the corpus callosum(by DTI analysis). These results showed that resting state fMRI and DTI suggest the same connectivity patterns in ADHD patients. It implies that the structural connectivity and the functional connectivity can influence each other. On the other hand, DTI also showed lower FA in the internal capsule, the corona radiata in ADHD patients, supporting the disruptions in motor and attention networks. The mismatches between the two connectivity types could be caused by: (1) the results of resting fMRI just focus on the decreased functional connected regions in the default mode network, and DTI results showed the whole brain white matter in this paper. (2) The functional connectivity might be linked by multiple segments of fiber tracts, and structurally connected regions might not be functionally connected. Future studies are needed to further explore the relationships between the changes of functional connectivity and structural connectivity in ADHD patients by DTI fiber tracking.

The present resting fMRI study also have confirmed the previously published results and provide further evidence to support that altered resting brain connectivity is involved in the neuropathology of ADHD (Castellanos et al. 2008; Uddin et al. 2008). Uddin et al. examined the default mode network by network homogeneity, and found reduced network homogeneity within the default mode network in ADHD subjects compared to age-matched controls, particularly between the precuneus and other default mode network regions (Castellanos et al. 2008; Uddin et al. 2008). This reduced resting state functional connectivity between the anterior and posterior regions of the DMN may indicate a relationship between working memory deficits and attention lapses in ADHD patients (Castellanos et al. 2008). Zang et al. used amplitude of low-frequency (0.01–0.08 Hz) fluctuation (ALFF) to investigate the baseline brain function of this disorder, and also found that patients with ADHD had decreased ALFF in the right inferior frontal cortex, left sensorimotor cortex, bilateral cerebellum and the vermis, but had increased ALFF in the right anterior cingulate cortex, left sensorimotor cortex, and bilateral brainstem (Zang et al. 2007). Despite differences in methodology, these findings all suggest that decreased functional interactions in the DMN may underlie some of the executive function deficits observed in the ADHD patients. On the other hand, an interesting finding of this study is the increased functional connectivity in bilateral posterior medial frontal cortex (pMFC). A review of primate and human studies, along with a meta-analysis of the human functional neuroimaging literature, suggested that the function of the pMFC is involved in performance monitoring, detection of unfavorable outcomes and response errors (Ridderinkhof et al. 2004a, b). ADHD children are abnormally and easily excitable or exuberant, and have strong emotional reactions or impulsive behavior, which may activate more pMFC to respond in the resting-state. These significant changes in DMN found in the ADHD patients may suggest the abnormalities of autonomic control and performance monitoring functions in them. By virtue of its non-invasiveness, high spatial and temporal resolution, low expense and clinical convenience, resting-state DMN could be an advantageous choice for ADHD pathology analysis. It is commonly assumed that functional brain connectivity reflects structural brain connectivity, and the strength of resting-state functional connectivity is positively correlated with that of structural connectivity (Damoiseaux and Greicius 2009). We also found that ADHD patients had significantly decreased functional connectivity in the anterior cingulate cortex, posterior cingulate cortex, lateral prefrontal cortex, left precuneus and thalamus, and had significantly decreased structural connectivity in the forceps minor, the internal capsule, the corona radiata, the optic radiation, and the splenium of the corpus callosum. However, functional connectivity is also observed between regions where there is little or no structural connectivity, which most likely indicates functional correlations mediated by indirect structural connections (i.e. via a third region) (Damoiseaux and Greicius 2009). For example, emerging evidence points to functional interactions between the pMFC and the lateral prefrontal cortex (LPFC), so that monitoring-related pMFC activity serves as a signal that engages regulatory processes in the LPFC to implement performance adjustments (Ridderinkhof et al. 2004a, b). However, little is known about the structural connectivity between the pMFC

and LPFC. Possibly, this functional interplay between the pMFC and LPFC is in part mediated by subcortical structures such as the basal ganglia (Ullsperger and von Cramon 2003) or by the supplementary motor area (SMA) or pre-SMA (Brass and von Cramon 2004). We found that ADHD patients had increased functional connectivity in pMFC but decreased connectivity in lateral prefrontal cortex (LPFC), which suggests that ADHD patients can probably monitor performance by pMFC but cannot implement performance adjustments by LPFC. The problem may be caused by LPFC or the third region such as the basal ganglia.

The approach to combine structural and functional connectivity data in ADHD as derived from resting-state fMRI and DTI is indeed a very interesting and promising method. However, there are still some limitations on these preliminary results such as the small sample size, and also some of the group differences may be chance findings due to the lack of full correction for multiple comparisons. Therefore, these preliminary results should be interpreted with caution. We still have much to learn about the developing human brain in ADHD and more replication will be needed to validate these initial observations. As the methodologies for measuring structural and functional connectivity continue to be improved and their complementary strengths are applied in parallel, we can expect important advances in diagnostic and prognostic capacities in ADHD.

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