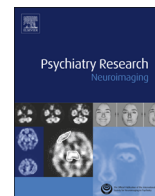




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# Abnormalities of structural covariance networks in drug-naïve boys with attention deficit hyperactivity disorder



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## ABSTRACT

The aim of this study is to investigate whether the anatomical organization of large-scale brain systems would change in ADHD patients compared to healthy controls. We utilized a structural covariance network (SCN) mapping approach to investigate large-scale networks in 30 drug-naïve ADHD boys and 30 gender- and age-matched controls. The regions showing significant between-group differences in gray matter (GM) volume were defined as seed regions of interest. Then, the SCNs derived from these seeds were statistically compared between ADHD and controls. Significant regional GM volume decreases ( $P < 0.05$ , corrected) were observed in the right insula and the right orbito-frontal cortex (OFC) in ADHD relative to controls. Both SCNs derived from these two seeds showed more localized topology in ADHD group. Furthermore, significantly decreased structural connectivity were found between insula and right hippocampus, bilateral olfactory cortex, and between OFC and bilateral caudate nucleus ( $P < 0.05$ , corrected) in ADHD group. Significantly increased association was observed between insula and left middle temporal gyrus ( $P < 0.05$ , corrected) in ADHD group. Taken together, our results reveal abnormal regional brain anatomy as well as aberrant structural covariance networks in ADHD, supporting previous findings of dysfunction in distributed network organization in patients with ADHD.

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## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. It is characterized primarily by developmentally inappropriate inattention, hyperactivity and/or impulsivity (Biederman, 1997). Although the neurobiology of ADHD remains unknown, accumulating evidence from structural and functional magnetic resonance imaging (MRI) studies indicates the presence of distributed brain region abnormalities in ADHD. Structural and functional abnormalities are consistently reported in the prefrontal cortex, basal ganglia, inferior parietal cortex and cerebellum (Cubillo et al., 2012; Frodl and Skokauskas, 2012; Hart et al., 2012); however, other brain regions, such as the temporal and occipital cortex, insula and

hippocampal gyrus, are also implicated in the pathophysiology of ADHD (Biederman, 2005; Bush et al., 2005). Recently, functional and anatomical connectivity studies, which explore systems-level relationships among brain regions, have indicated abnormalities in large-scale brain systems in ADHD (Castellanos and Proal, 2012).

Functional connectivity, which explores the correlation of regional functional MRI (fMRI) signals across time from different brain regions, has been widely used to explore the pathophysiology of ADHD and has indicated a number of different neural systems abnormalities in ADHD, including abnormalities in prefrontal-striatal circuits and the default-mode network (Cao et al., 2009; Castellanos et al., 2008; Castellanos and Proal, 2012; Sun et al., 2012). Diffusion tensor imaging (DTI) explores connectivity in vivo by inferring the structural connectivity between brain regions and examining the microstructural integrity of white matter tissue (Le Bihan, 2003). Studies employing DTI have revealed widespread changes in white matter integrity in ADHD, most consistently in the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum (all of which were previously implicated in the ADHD pathophysiology) (van Ewijk et al., 2012). However, many concerns remain regarding DTI

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methodology, such as its bias against longer paths, diminished resolution of crossing fibers and sensitivity to algorithm and parameter choice (Evans, 2013).

Structural covariance networks (SCNs), derived from voxel-based morphometry (VBM), represent a complementary addition to fMRI and DTI connectivity analyses. SCNs characterize the pattern of covariance between the GM volume of a region of interest and the GM volumes of other regions throughout the entire brain using a general linear model framework (Mechelli et al., 2005; Montembeault et al., 2012; Soriano-Mas et al., 2013; Zielinski et al., 2010). This covariance of GM volume in different cortical regions is thought to result from mutually trophic influences (Ferrer et al., 1995) or shared experience-related plasticity (Draganski et al., 2004; Mechelli et al., 2004). Structural covariance is also thought to partially reflect connectivity between cortical regions, such as physical connectivity via white-matter tracts (Evans, 2013). Gong et al. reported about 35–40% of GM thickness correlations are convergent with fiber connections (Gong et al., 2012). In addition, Seeley et al. (2009) reported the SCNs have been shown to recapitulate functional brain network topologies of synchronously activated regions. These findings provide substantial support for the use of SCNs to measure network integrity for cross-sectional group studies. To date, SCNs analyses have successfully explored changes in brain connectivity in different neuropsychiatric disorders, such as autism and obsessive-compulsive disorder (Cardoner et al., 2007; McAlonan et al., 2005; Nosarti et al., 2011). However, it remains unknown whether the anatomical organization of large-scale brain systems is altered in ADHD patients relative to healthy controls.

Here, we utilized an SCN mapping approach to investigate large-scale networks in 30 drug-naïve ADHD boys and 30 gender- and age-matched controls. We only included drug-naïve patients in this study because previous studies have suggested that stimulants can significantly influence the structure and function of the brain in ADHD (Bush et al., 2008; Shaw et al., 2009). We first defined seed regions of interest (ROIs) by identifying regions showing significant between-group differences in GM volume using VBM. Then, we constructed the SCNs on the basis of the correlations among the volume of each seed ROI and GM volumes of other regions throughout the whole brain. Given that inter-connecting brain systems have common influences on development and maturation (Cheverud, 1982, 1984), we expect that ADHD patients may have altered GM networks compared to controls.

## 2. Methods

### 2.1. Participants

This study included 30 drug-naïve ADHD patients (8–14 years) recruited from the outpatients at the Institute of Mental Health of Peking University and 30 age-matched controls (8–14 years). For each participant, a semi-structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)(Kaufman et al., 1997) (based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), was administered to diagnose ADHD; the scores of the ADHD Rating Scale-IV (ADHD RS-IV) were reported by the parents. The ADHD RS-IV contains all the inattention and hyperactivity/impulsivity symptoms of ADHD described in the DSM-IV. Each symptom is scored according to the frequency with which it occurs (i. e., “never” is rated as 1, “occasionally” is 2; “often” is 3; “always” is 4) (DuPaul et al., 1998). Following a detailed explanation of the study procedure, written informed consent was obtained from all parents or guardians of participants. All children agreed to participate in this study. The demographic information and clinical characteristics of the participants are presented in Table 1. This study was approved by the Research Ethics Review Board of the Institute of Mental Health, Peking University.

The inclusion criteria for ADHD included the following: (i) predominantly inattention type (ADHD-I) or combined type (ADHD-C); (ii) right-handedness, as assessed by the Chinese Handedness Inventory (Xin-tian, 1983); (iii) no lifetime

**Table 1**

Demographic characteristics of control and ADHD participants.

	Control (n=30)	ADHD (n=30)	t-Value	df
Age (Years)	10.3 ± 1.6	10.3 ± 1.9	0.07	58
Inattention scores <sup>a</sup>	17.5 ± 3.9	27.5 ± 3.9	−10.16	56 <sup>a</sup>
Impulsivity scores <sup>a</sup>	15.6 ± 3.9	23.9 ± 10.0	−4.19	56 <sup>a</sup>
IQ <sup>a</sup>	121.7 ± 14.0	107.1 ± 14.4	3.97	58

All subjects were right-handed boys. The values are the mean ± standard deviation. All variables were compared with two-sample *t*-tests.

<sup>a</sup> Two normal participants missed these scores.

\* *P* < 0.001.

history of head trauma with loss of consciousness; (iv) no history of neurological illness, significant head trauma or other severe diseases; (v) no history of emotional disorders, affective disorders, Tourette disorder or other Axis I psychiatric disorder; (vi) no evidence of severe language development delay or communication problems as determined through clinical history, parental interview, and observation of the children; (vii) full scale IQ higher than 80 as measured by the Wechsler Intelligence Scale for Chinese Children-Revised (WISCC-R) (Gong and Cai, 1993). The inclusion criteria for the controls were the same as those for the ADHD group with the exception of ADHD diagnosis. Half of the patients met the criteria for ADHD-I, and the other 15 met the criteria for ADHD-C. Eleven patients with comorbid oppositional defiant disorder (ODD) were not excluded from the study.

### 2.2. Image acquisition

MR imaging was carried out on a SIEMENS TRIO 3T scanner. High-resolution 3D T1-weighted images were sagittally acquired using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence: repetition time (TR)=2530 ms; echo time (TE)=3.39 ms; inversion time=1100 ms; flip angle=7°; field of view (FOV)=256 mm × 256 mm; matrix=256 × 256; 128 slices, thickness=1.33 mm. Additional scanning sessions (i.e., DTI) (Cao et al., 2013) with the current participants were acquired with whole brain coverage using a shingle-shot echo planar imaging sequence: slice thickness=2.5 mm with no interslice gap, TR=7200 ms, TE=104 ms, flip angle=90°, 64 diffusion directions with *b*=1000 s/mm<sup>2</sup>, and an additional image without diffusion weighting (i.e., *b*=0 s/mm<sup>2</sup>), matrix=128 × 128, FOV=230 mm × 230 mm, average=1.

### 2.3. Image processing

Structural images were processed using an optimized VBM method. The data were analyzed using the standard parameters of the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in Statistical Parametric Mapping software (SPM 8; The Wellcome Department of Imaging Neuroscience, London, UK) running on Matlab 7 (MathWorks Inc., Natick, Mass, MA, USA). Briefly, the whole-brain MR images were segmented by tissue type (GM, white matter, cerebrospinal fluid) using an adaptive maximum a posteriori technique (Rajapakse et al., 1997) and a partial volume estimation method (Tohka et al., 2004), eliminating the need for *a priori* tissue probability information. In addition, a spatially adaptive non-local denoising filter (Manjón et al., 2010) and a hidden Markov random field model (Rajapakse et al., 1997) were applied to minimize the level of noise in the resulting GM segments. Then, we created our own customized tissue probability maps (TPMs) using the Template-O-Matic toolbox (<http://dbm.neuro.uni-jena.de/software/tom/>). By including the demographic variables of our sample in the template, the average age and gender were calculated and a fitting average template was created accordingly (Wilke et al., 2008). Subsequently, all images were registered to the customized TPMs using a diffeomorphic anatomical registration using exponential lie algebra (DARTEL) approach (Ashburner, 2007). Furthermore, modulated GM values were generated using non-linear components of the Jacobian determinants derived from the spatial normalization step to preserve the total amount of GM from the original images (Good et al., 2002). Finally, the resulting GM images were smoothed with an isotropic Gaussian kernel of 12 mm full width at half maximum.

### 2.4. Definition of the region of interest

Two-sample *t*-test was conducted to find between-group differences in GM volumes in ADHD relative to controls. The intracranial volume (ICV) and age were entered as variables of no interest. To remove the effect IQ difference on the pattern of SCN, IQ score was also entered as a confounding variable. In addition, due to 36.7% of our ADHD participants with comorbid ODD, a diagnostic variable (1 for no comorbidities, and 2 for comorbid ODD) was also treated as a confounding covariate (Sasayama et al., 2010). The statistical result was corrected for multiple comparisons with Monte Carlo simulations using the REST AlphaSim program (free download from <http://restfmri.net/forum/REST>); this is a non-parametric and non-

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