Increased fractional anisotropy in white matter of the right frontal region in children with attention-deficit/hyperactivity disorder: A diffusion tensor imaging study

Qianqian Li *1,2, Jinhua Sun *1,3, Lanting Guo 1, Yufeng Zang 4, Zhengzi Feng 5, Xiaoli Huang 6, Hong Yang 6,7, Yating Lv 4, Mingjin Huang 1, Qiyong Gong 6

1 Dept. of Psychiatry, West China Hospital, Sichuan University, Guo Xue Xiang No.37, Chengdu, 610041, Sichuan Province, P.R. China; 2 Dept. of Psychiatry, the First Affiliated Hospital of Chongqing Medical University, You Yi Lu No.1, Chongqing, 400016, P.R. China; 3 Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 Wan Ping Nan Road, Shanghai 200030, P.R. China; 4 State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Xin Jie Kou Wai Da Jie No.19, Beijing,100875, P.R. China; 5 Mental health and education center, Third Military Medical University, Gao Tang Yan Zheng Jie No.30, Chongqing, 400030, P.R. China; 6 MR Research Center, Dept. of Radiology, West China Hospital, Sichuan University, Guo Xue Xiang No.37, Chengdu, 610041, Sichuan Province, P.R. China; 7 Dept. of Radiology, First Affiliated Hospital of College of Medical Science, Zhejiang University, Yu Hang Tang Lu No.388, Hangzhou, 310058, P.R. China.

*Dr. Qianqian Li and Jinhua Sun contributed equally to the study.

Correspondence to: Lanting Guo, MD., Department of Psychiatry, West China Hospital, Sichuan University, Guo Xue Xiang No.37, Chengdu, 610041, P. R. China. tel: +86 28 18980601720; e-mail: guolanting@sina.com; guolanting@yahoo.com

Submitted: 2010-06-08 Accepted: 2010-10-10 Published online: 2010-12-25

Key words: attention-deficit/hyperactivity disorder; diffusion tensor imaging; white matter; children; magnetic resonance imaging; executive function

Abstract

OBJECTIVE: Abnormalities of frontal white matter (WM) have been found in some children with ADHD. The purpose of this study was to explore the changes in WM in child patients with ADHD by DTI, which detects changes in WM microstructure based on properties of diffusion. We also expect to investigate the relationship between the changes in WM and executive function in child patients with ADHD.

METHODS: DTI was performed on 24 patients with ADHD and 20 healthy controls. A series of neuropsychological tests and a structural interview were conducted to assess the cognitive functions and clinical data of the ADHD patients and controls.

RESULTS: Firstly, child patients with ADHD have higher fractional anisotropy (FA) values in WM in the right frontal region. Secondly, FA in right frontal WM is positively correlated with scores in the Stroop test.

Conclusions: Increased FA of right frontal WM implies a higher degree of myelination and lower degree of neural branching in WM, contributing to the neurological deficits of ADHD.
INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by age inappropriate symptoms of inattention and/or hyperactivity or impulsivity which occur for at least 6 months in at least two domains of life and begin prior to the age of 7. It is estimated that ADHD affects approximately 8% to 12% of school-aged (6–12 years) children and 4% of adults (Murphy & Barkley 1996; Faroene et al. 2003).

The etiology of ADHD remains unclear. ADHD is increasingly conceptualized as a disorder of abnormal neuronal circuitry fundamentally important for attentional and cognitive control. The neuronal circuitry involves frontal, striatal, and parietal areas (Giedd et al. 2001). The frontal area is the center of this network and the most consistently reported region of structural functional difference in ADHD.

In recent years, the executive functions have been applied as a concept to help explain ADHD pathophysiology. As Russell Barkley explains, executive functions, which are modulated by the prefrontal cortex, are thought to enable a person to successfully engage in independent, purposeful, and self-serving behaviors.

Some executive function tasks were selected to measure the four major domains of executive function (interference control, visual working memory, cognitive flexibility, and verbal fluency). Interference control refers to the ability to monitor response conflict and suppress a competing response in order to carry out a primary response. It was operationalized with the Stroop Color-Word Interference Test (Golden 1976), which evaluates interference control rather than naming speed. Stroop variables include the mean reaction time for Color–Word, the number answered right, the number of errors, and the number of corrections (answers named wrong at first and corrected immediately). The Wisconsin Card Sorting Test is a widely used measure to tap cognitive flexibility (Heator et al. 1981). The dependent variables of interest are the total number of errors and categories. Verbal fluency was measured by the capacity to generate novel responses (Benton et al. 1978). The dependent measure in this task was the total number of error words. The visual memory test measured both immediate and delayed visuo-spatial memory abilities (Wechsler 1987). In the test, each design contained one or more figures. Each of these designs was presented to the child for 10 seconds. The child was then required to reproduce the designs both immediately after they were presented and 30 minutes later.

Some studies indicate that abnormalities in the prefrontal cortex may be an important cause of ADHD. A study conducting a meta-analysis of structural imaging showed that it is more common that the volume of the prefrontal region (including gray and white matter), corpus callosum, the right caudate nucleus, etc. was decreased in patients with ADHD (Valera et al. 2007).

However, one study found that no brain structures were significantly different between the ADHD group and control group (Overmeyer et al. 2001). Even more interesting is that another study found that in children with ADHD, frontal lobe volume was increased, and the increased volume showed a positive correlation with the symptoms of ADHD (Sowell et al. 2003). The reasons for these inconsistent results still need further study.

White matter is one of the two components of the central nervous system and consists mostly of myelinated axons, which is the physiological basis of the link between different regions of the cortex and the link between the cortex and subcortical structures.

Many studies have found that the abnormal development of WM in patients with ADHD may be an important factor in its pathophysiology. Using MRI, researchers found that compared to the control group, ADHD patients showed decreases in WM volume (Filipek et al. 1997; Overmeyer et al. 2001; Castellanos et al. 2002; Mostofsky et al. 2002).

Research methods that are more sensitive than MRI, such as diffusion tensor imaging (DTI) technology, have also started to be used for the detection of ADHD in patients through brain WM structure. Diffusion tensor imaging (DTI) is an MRI technique for detecting water molecules in vivo in different organizations, as well as WM fiber tracts in the case for diffusion, and can reflect the micro-features of the structure of the nerve fibers (Klingberg T 1999).

Currently, there are six articles on the white matter of patients with ADHD that use DTI techniques, and the results are varied. The regions involved are the anterior corona, left fronto-temporal region, right parietal-occipital regions, cingulum bundle, right premotor, right striatal, and cerebellum (Ashtari et al. 2005; Casey et al. 2007; Hamilton et al. 2008; Makris et al. 2008; Pavuluri et al. 2009; Silk et al. 2009).

In this study, we used DTI to investigate WM integrity and the microstructure of WM in children with ADHD relative to age- and gender-matched control subjects. We also expect to explore the relationships between abnormalities of WM and cognitive function in children with ADHD.

MATERIALS AND METHODS

Participants

After a complete description of the study to the subjects and their parents, written assent and consent were obtained. Participation in this study did not interfere with treatment. Subjects underwent an MRI scan, a diagnostic interview, and a neuropsychological test battery. The battery consisted of the Wechsler Intelligence Scale for Children – Chinese Revision (WISC-CR) (Dai Xiaoyang & Gong Yaoxian 1990), Stroop test, verbal fluency test, and modified Wisconsin Card sorting test. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield 1971); patients’ emotional...
and behavioral problems were assessed by the Conners' Parent Rating Scale-Revised: Short version (Conners 1999) and the DSM-IV (American Psychiatric Association, 1994).

24 patients with ADHD, 22 male and 2 female, were recruited from the Clinic of Psychiatry Department of West China Hospital. The patients were diagnosed by two experienced clinicians according to the standard criteria of DSM-IV, and all subjects underwent an extensive psychiatric and neurological examination. Psychiatric diagnoses were formed on the basis of structured interviews (Kiddie-Sads-Present and Lifetime Version 1.0, Kaufman et al. 1996). The inclusion criteria were: 1) WISC-CR full-scale IQ > 70; 2) ratings of core ADHD symptoms ascertained by at least 2 SDs above age- and gender-specific means on both the inattentive and hyperactive-impulsive subscales of the parent version of the CADS (Goyette et al. 1978); 3) aged 6–16 years. The exclusion criteria were: 1) any previous psychotropic medication administration; 2) evidence of neurologic or endocrine disorders on examination or by clinical history; 3) any other Axis I psychiatric disorder requiring treatment with medication; 4) any contraindications to MRI scanning (e.g., metal implants, pacemakers); 5) parental history of a significant Axis I or II psychiatric disorder in their first degree relatives. All of the children with ADHD were drug-naive.

20 control subjects were recruited from local schools with similar education levels to those of the ADHD subjects. They were interviewed by a trained research assistant using the Kiddie-Sads-Present and Lifetime Version 1.0. All controls were screened for inattentiveness, overactivity, and/or impulsiveness by the same tests applied to the ADHD patients. The exclusion criteria for control subjects were: 1) an Axis I or II psychiatric disorder; 2) WISC-CR full-scale IQ < 70; 3) ongoing medical or psychiatric disorders; 4) parental history of a significant Axis I or II psychiatric disorder in their first degree relatives.

ADD: All subjects provided written informed consent following a protocol approved by the Sichuan University Ethics Committee and the Research Ethics board at the West China Hospital.

MRI Procedures
MRI was undertaken on a 3.0 T GE MR scanner (SIGNA EXCITE, General Electric, Milwaukee, USA) at the West China Hospital. DTI was carried out using echo-planar (EPI) acquisition at 3.0 T. Axial DTI slices were obtained with following parameters: TR = 10000 ms, TE = 70.8 ms, flip angle = 12°, slice thickness = 3 mm, FOV = 24×24 cm, matrix = 128×128, voxel size = 3×3×3 mm³, b = 1000 s/mm² and NEX = 2.

Image Processing
Image analysis was run on SPM2 (statistical parametric mapping) software (http://www.fil.ion.ucl.ac.uk/spm).

Diffusion Tensor Imaging
Fractional anisotropy (FA) was determined for every voxel according to standard methods. A customized template was obtained by taking the average of all participants’ T2 (b = 0) images, which had been previously normalized to the EPI template within standard stereotactic space. These b = 0 scans were implicitly in the same raw image space as the generated FA maps and can be used to register individual data into standard anatomical space to allow voxel-by-voxel statistical analysis of diffusivity indices among subject groups. Both T2 images and FA maps were normalized by means of a customized template. This procedure provided a mechanism of registering all participants’ data in native image space. To generate GM, WM, and CSF masks for tissue segmentation, the T2 normalized images were then segmented. The masked FA maps were smoothed with an 8 mm FWHM kernel.

Statistical Analysis
Statistical analysis was conducted using statistical software (SPSS13.0, http://www.spss.com). Differences among groups at baseline were examined using a two-sample t test for continuous variables and χ² tests of independence for categorical variables. The level of significance was set at p < .0001. A partial correlation analysis was performed to value the relationship between executive function and brain structure change in ADHD patients.

RESULTS
Participants
24 patients with ADHD (mean age ± SD = 9.62 ± 2.19 years, ranging from 7 to 13), 22 male and 2 female, were recruited from the Clinic of Psychiatry Department of West China Hospital. 20 control subjects (mean age ± SD = 10.12 ± 1.83 years, ranging from 7 to 13), 18 male and 2 female, were recruited from local schools with similar education levels to those of the ADHD subjects. There were no significant differences between the patients and controls in mean age and proportion who were strongly right-handed.

Neuropsychological Tests Results
1) The ADHD patients’ visual memory scores were significantly lower than those of the controls (p<0.01); 2) In the Stroop test, the mean reaction time of the ADHD group was longer than that of the controls (p<0.05); 3) The number of errors of the ADHD group was higher than that of the controls (p<0.05); 4) Hyperactivity scores of the ADHD patients were significantly higher than those of the controls (p<0.01).
Compared to the controls, increased FA was found in ADHD patients in right frontal WM (Figure 1).

**The relationship between the neuropsychological tests and brain structure**

The correlation of scores for the visual memory test, Stroop test, verbal fluency test, modified Wisconsin Card Sorting Test, and FA whole-brain histograms with the clinical scales scores are detailed in Tables 4 and 5.

In ADHD patients, in the Stroop test, the number right and number of corrections were positively correlated with FA in right frontal WM. In the verbal fluency test, the number of errors was negatively correlated with FA in right frontal WM.

In controls, the number of corrections in Stroop was positively correlated with FA in right frontal WM and hyperactivity was negatively correlated with FA in right frontal WM.

**DISCUSSION**

In this study, DTI was adopted in an attempt to shed light on the abnormalities of WM and the relationship between the abnormalities and cognitive function in ADHD. DTI measures the displacement of water molecules across tissue components, providing information regarding the microstructure of cerebral WM. FA is a normalized measure of diffusion anisotropy that provides information about the degree of fiber organization and integrity. FA yields values between 0 (isotropic or unrestricted diffusion, as in cerebrospinal fluid) and 1 (anisotropic or restricted diffusion due to barriers, as in organized WM fibers).

We found that DTI analysis showed patients with ADHD had higher FA in right frontal WM.

The total brain volume changes during late childhood and adolescence mask complex changes in WM.
Maturational increases in WM are assumed to be present globally, with specific increases shown in the frontal, parietal, and occipital lobes (Sowell et al. 2002a; Sowell et al. 2002b). The increase of WM volume with growing age suggests that the decline in gray matter density (GMD) until age 40 is related to an increase of cerebral myelination (Sowell et al. 2003). During late childhood and adolescence, nerve fibers continue to extend and neuronal connections are pruned as children adapt to the environment (Reiss et al. 1996; Giedd et al. 1999; Courchesne et al. 2000; Sowell et al. 2002a).

Recently, reductions in both GM and WM have been found in the left and right prefrontal cortex in ADHD patients (Filipek et al. 1997; Overmeyer et al. 2001; Kates et al. 2002).

In contrast to these studies, Pueyo et al. found that the ADHD group showed a higher WM signal intensity ratio, probably reflecting a higher degree of myelination (Pueyo et al. 2003).

Several lines of evidence suggested that abnormalities in right frontal WM development might be an important factor in the pathophysiology of ADHD (Casey et al. 2007). The prefrontal cortex has been shown to be significantly smaller in ADHD children than in controls (Castellanos et al. 1996; Filipek et al. 1997; Kates et al. 2002; Mostofsky et al. 2002; Durston et al. 2003, 2004; Krain & Castellanos 2006; Mackie et al. 2007; Castellanos et al. 2008; Mulder et al. 2008; Buderath et al. 2009). The frontal cortex was associated with social disinhibition, impulse dyscontrol, and organization, planning, working memory and attention dysfunctions.

Castellanos et al. found that frontal and cerebellar volumes were significantly negatively correlated with global clinician ratings and parent ratings of child attention problems (Castellanos et al. 2002; Perlov et al. 2008).

We found that participants with ADHD showed higher FA in right frontal WM, which may represent a possible neural basis for some of the motor and attentional deficits commonly found in ADHD. In our study, exploratory analyses were conducted to examine the relationship between the severity of ADHD symptoms/neuropsychological functioning and abnormalities of WM in children with ADHD and controls. We found that FA in right frontal WM in ADHD patients was higher than in controls. We also found that the FA values in the right frontal region in children with ADHD were positively correlated with executive functions and negatively correlated with hyperactivity scores.

Most previous studies show that smaller brain volumes of white matter are associated with worse executive function and more serious clinical symptoms. (Semrud-Clikeman et al. 2000; Castellanos et al. 2002). However, some studies have reached the opposite conclusion: the greater the prefrontal volume, the worse the level of executive function (Hill et al. 2003; Sparkes et al. 2004). These previous studies on ADHD using DTI implied that, compared with normal children, patients with ADHD have lower FA values in WM, which may be caused by impairment of myelinated nerve sheaths and thus might influence information transmission and reduce cognitive function.

However, in our study, we found that the patients with ADHD have higher FA values than normal chil-
Qianqian Li, Jinhua Sun, Lanting Guo, Yufeng Zang, Zhengzi Feng, Xiaoli Huang, Hong Yang, Yating Lv, Mingjin Huang, Qiyong Gong

ACKNOWLEDGEMENTS

This study was supported by Doctoral Program Foundation of Institutions of Higher Education of China (JS 20050610068), and Natural Science Foundation of China (NSFC 30621130074). Preliminary data of this article were collected at the Department of Psychiatry of West China Hospital, Sichuan University.

REFERENCES


CONCLUSION

The excessive hyperplasia of myelination of neural fibers in white matter in some important regions of brain may be due to a compensatory mechanism for ADHD.


