ORIGINAL ARTICLE

Increased Fractional Anisotropy in White Matter of the Right Frontal Region in Children with Attention-Deficit/Hyperactivity Disorder: A Diffusion Tensor Imaging Study

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Abstract

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. 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. 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; Faraone *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 struc-

tured 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 = 10 000 ms, TE = 70.8 ms, flip angle = 12 °, slice thickness = 3 mm, FOV = 24×24 cm, matrix = 128×128, voxel size = 3×3×5 mm^3, b = 1 000 s/mm^2 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 χ^2 tests of independence for categorical variables. A χ^2 test was used to determine the difference between the ADHD and control groups in clinical details. A two-sample t test was performed to determine significant differences between the two subject groups for clinical outcome variables, WM regions, and each voxel on the corrected FA values. 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).

Diffusion Tensor Imaging Analysis

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.

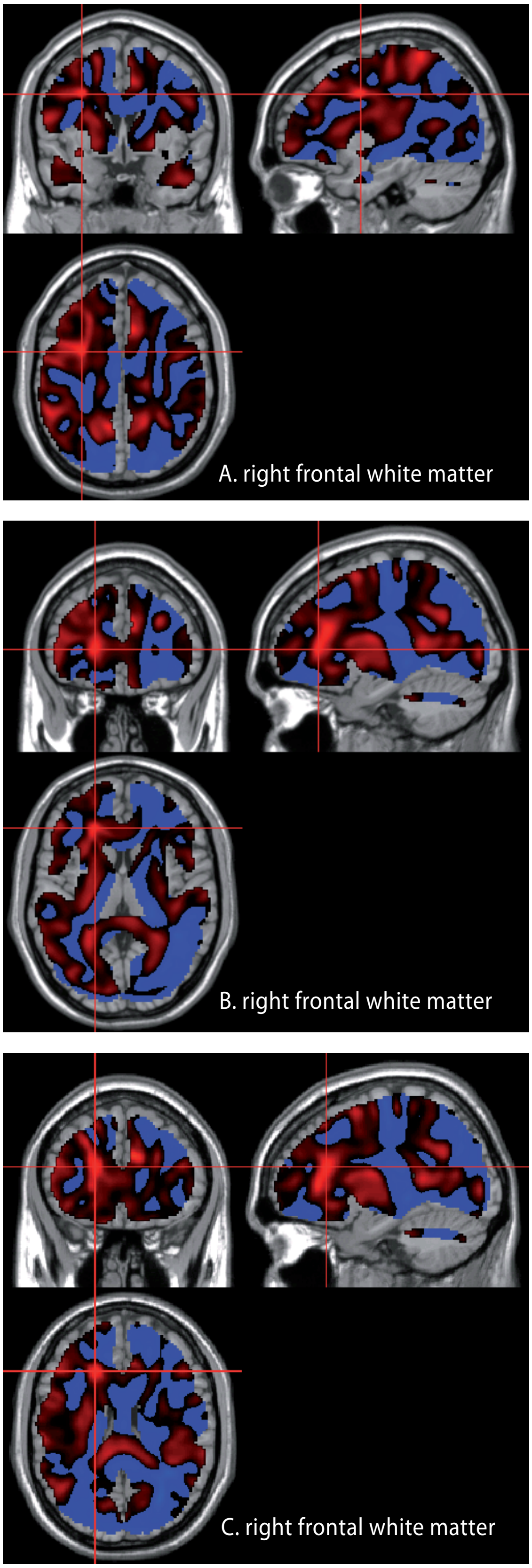

Fig. 1. Maps of significant clusters representing regions of increased FA in patients with ADHD. The specific involvement of right frontal white matter (panel A), right frontal white matter (panel B), right frontal white matter (panel C). The threshold was set at T = 3.32.

Tab. 1. Demographic and Clinical Details of patients and control.

	Patient (n=24)	Control (n=20)	Test of Significance
Age Mean (SD)	9.62 (2.19)	10.12 (1.83)	t=0.754 p>0.05
Sex M:F No	22:2	18:2	χ^2=0.01 p>0.05
Strongly right-handed. No (%)	21 (87.5)	18 (90)	χ^2=0.47 p>0.05
DSM-IV diagnosed disorders No. (%)			
Combined type	18 (75)		
Inattentive subtype	6 (25)		
Comorbidity, No. (%)			
Oppositional defiant disorder	8 (33)		

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

Tab. 2. Clinical outcome variables of patients and control.

		Patient (n=24) Mean (*SD*)	Control (n=20) Mean (*SD*)	*p*-Value for Patients vs Controls
visual memory	no delay	15.33 (3.09)	21.15 (1.98)	.000
visual memory	30-minute delay intervals	12.71 (5.11)	20.42 (2.27)	.001
Stroop	mean reaction time	91.85 (18.82)	71.84 (17.36)	.035
Stroop	number right	55.21 (21.26)	63.92 (11.64)	.176
Stroop	number errors	5.52 (5.08)	2.14 (2.04)	.026
Stroop	number correction	4.26 (2.32)	4.85 (2.68)	.502
verbal fluency test	number errors	1.09 (1.04)	0.90 (1.04)	.746
WCST	categorization	3.87 (1.41)	4.85 (1.61)	.118
Conner	Hyperactivity	16.88 (3.89)	4.86 (2.80)	.000

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.

Tab. 3. Significant clusters identified with increased fractional anisotropy in children with attention-deficit/hyperactivity disorder as compared with normal control subjects.

Anatomic Definition	T	X	Y	Z
right frontal white matter	4.38	30	2	34
right frontal white matter	3.98	20	34	6
right frontal white matter	3.93	20	28	20

Height threshold: T=3.32, *p*=0.001

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 children in WM of the frontal region, and FA is positively related with cognitive function both in patients and normal children. Thus we can infer that the myelinated nerve sheaths of ADHD children originally had defects. However in the process of adapting to their surroundings, the myelinated nerve sheaths exhibit excessive hyperplasia, which leads to excessive, thick myelin in some ADHD children, leading to a high FA value of WM. However, the excessive, thick myelin of

Tab. 4. Spearman rank correlation (*p*) values between Stroop test, verbal fluency test, modified Wisconsin Card sorting test, and Fractional Anisotropy in ADHD patients.

variable	X	Y	Z	visual memory			STROOP			verbal fluency test	WCST	conner
Fractional Anisotropy				no-delay	30-minute delay intervals	number errors	Mean reaction times	Number right	Number correction	number errors	categorization	Hyperactivity
right frontal white matter	30	2	34	0.277	0.154	0.044	−0.404	0.489	0.156	−0.501	0.270	0.079
								p=0.034		p=0.021		
right frontal white matter	20	34	6	0.088	−0.024	−0.278	−0.133	0.111	0.095	−0.115	0.040	−0.070
right frontal white matter	20	28	20	0.265	0.060	−0.062	−0.440	0.229	0.504	0.107	0.079	−0.158
									p=0.028			

Tab. 5. Spearman rank correlation (*p*) values between Stroop test, verbal fluency test, modified Wisconsin Card sorting test , and Fractional Anisotropy in controls.

variable	X	Y	Z	visual memory			STROOP			verbal fluency test	WCST	conner
Fractional Anisotropy				no-delay	30-minute delay intervals	number errors	Mean reaction times	Number right	Number correction	number errors	categorization	Hyperactivity
right frontal white matter	30	2	34	−0.038	0.049	0.243	0.127	0.045	−0.396	0.186	−0.097	−0.564
												p=0.023
right frontal white matter	20	34	6	−0.125	0.113	0.026	0.459	−0.380	0.369	0.030	−0.505	0.283
right frontal white matter	20	28	20	0.186	0.251	−0.368	0.158	−0.316	0.589	−0.063	−0.413	0.502
									p=0.027			

the myelinated nerve sheaths cannot completely compensate for the defective cognitive function of ADHD children, so the cognitive function of ADHD children is still worse than that of normal children.

Therefore, the integrity of myelin and the excessive hyperplasia of the myelin sheaths of nerve fibers may both contribute to cognitive deficits in ADHD.

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.

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