

Attention-Deficit/Hyperactivity Disorder: A Preliminary Diffusion Tensor Imaging Study

Manzar Ashtari, Sanjiv Kumra, Shree L. Bhaskar, Tana Clarke, Emily Thaden, Kelly L. Cervellione, Joseph Rhinewine, John M. Kane, Andrew Adesman, Ruth Milanaik, Joseph Maytal, Alan Diamond, Philip Szeszko, and Babak A. Ardekani

Background: The purpose of this study was to explore whether there are white matter (WM) abnormalities in children with attention-deficit/hyperactivity disorder (ADHD) using diffusion tensor imaging. Based upon the literature, we predicted decreased fractional anisotropy (FA) findings in the frontal and cerebellar regions.

Methods: Eighteen patients with ADHD and 15 age- and gender-matched healthy volunteers received DTI assessments. Fractional anisotropy maps of WM were compared between groups with a voxelwise analysis after intersubject registration to Talairach space.

Results: Children with ADHD had decreased FA in areas that have been implicated in the pathophysiology of ADHD: right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas.

Conclusions: These preliminary data support the hypothesis that alterations in brain WM integrity in frontal and cerebellar regions occur in ADHD. The pattern of decreased FA might implicate the corticopontocerebellar circuit in the pathophysiology of ADHD.

Key Words: Attention-deficit/hyperactivity disorder, diffusion tensor imaging, white matter, children, magnetic resonance imaging

Attention-deficit/hyperactivity disorder (ADHD) is conservatively estimated to occur in 3%–6% of children, with an overrepresentation of boys by approximately 3:1 (Anderson et al 1987; Baumgartel et al 1995; Bird et al 1988). Attention-deficit/hyperactivity disorder is increasingly conceptualized as neurodevelopmental in origin. Although the mechanisms behind such altered development are not fully understood, they are likely to be complex. Currently, there is some controversy as to whether ADHD is a brain disorder of the right hemisphere (Heilman et al 1991; Stefanatos and Wasserstein 2001) or, alternatively, a common developmental abnormality that encompasses a number of parallel circuits (Mostofsky et al 2002). The latter would include neuronal circuits that connect the frontal lobe to the striatum, which are thought to mediate motor, oculomotor, cognitive “executive” functions, and socially responsive behavior (Mega and Cummings 1994), and/or circuits that connect the frontal lobe to the cerebellum (Middleton and Strick 2001).

Several lines of evidence suggest that abnormalities in white matter (WM) development might be an important factor in the pathophysiology of ADHD. White matter provides the physical foundation for corticocortical and subcortico-cortical connectivity. With regard to WM magnetic resonance structural abnormalities in ADHD, there has been a striking convergence of results. Anatomic magnetic resonance imaging (MRI) studies with different methodologies have consistently found that ADHD is associated with a 4%–6% decrease in WM volume throughout the

From the Departments of Radiology (MA, TC, AD) and Pediatric Neurology (JM), North Shore Long Island Jewish Medical Center; Developmental and Behavioral Pediatrics (AA, RM), Schneider Children’s Hospital, New Hyde Park; Department of Psychiatry Research (SK, SLB, ET, KLC, JMK, JR, PS), Zucker Hillside Hospital, Albert Einstein College of Medicine, Bronx; and Nathan S. Kline Institute for Psychiatric Research (BAA), Center for Advanced Brain Imaging, Orangeburg, New York.

Address reprint requests to Dr. Manzar Ashtari, Ph.D., Long Island Jewish Medical Center, C Level, Research Building, Department of Radiology, 270-05 76th Avenue, New Hyde Park, NY 11040; E-mail: ashtari@lij.edu.

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brain (Castellanos et al 2002, Filipek et al 1997; Hynd et al 1990; Mostofsky et al 2002; Overmeyer et al 2001). As reflected in Table 1, WM abnormalities have been reported across studies with diverse image analysis techniques and subject populations.

Studies have included boys and girls (Castellanos et al 2002) and prepubertal subjects (Mostofsky et al 2002; Overmeyer et al 2001) and have carefully excluded patients with comorbid disorders (Filipek et al 1997). Together, these data support a working hypothesis that the pathophysiology of ADHD might include abnormalities in WM development.

In a controlled study of 152 children and adolescents with ADHD (age range, 5–18 years) and 139 age- and gender-matched control subjects (age range, 4–19 years), Castellanos et al (2002) examined longitudinal growth curves of brain development for patients and control subjects of both genders. Developmental curves were significantly higher in control subjects than in ADHD patients for total WM volume. The authors suggest that additional studies are needed with more sensitive MRI techniques, such as diffusion tensor imaging (DTI), to detect localized anatomic abnormalities in fronto-cortical regions in never-medicated patients with ADHD.

Diffusion tensor imaging is an MRI technique used to examine water diffusion in different tissue and the organization of WM tracts in vivo (Conturo et al 1999). The brain’s anatomic connectivity is based on neuronal processes and their projections. The working hypothesis of the present study is that the pathophysiology of ADHD is likely to involve significant changes at the level of interconnections between two or more regions within a network (macroconnectivity). Unlike standard structural MRI techniques, DTI allows measurement of the microstructural features of WM and permits the study of fiber connections among anatomically and functionally defined brain regions (Conturo et al 1999; Makris et al 1997). Thus, it provides an assessment of macroconnectivity. With the DTI technique, the magnetic resonance signal is sensitized to the movement of water on a microscopic level, and the magnitude and direction of the water diffusion in three dimensions is determined (Basser 1995; Basser et al 1994). In WM, water diffusion is greater along fiber tracts than it is perpendicular to the direction of the axons, where it is restricted by the myelin sheath and cell membrane (Moseley et al 1990). This is termed anisotropic diffusion; free water has an isotropic distribution.

Diffusion-weighted MRI has great potential for studying cerebral WM diseases because of its inherent sensitivity to water diffusion

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Table 1. Summary of Structural Magnetic Resonance Imaging Studies in Attention-Deficit/Hyperactivity Disorder

Study	N and Age (years)	Segmentation Method/Areas Examined	Principal Findings in ADHD
Castellanos et al 2002	152 ADHD (63 females) Age: 5–18 139 NC (56 females) Age: 4.5–19	Automated segmentation Volumes of GM and WM in frontal, temporal, parietal, occipital lobes, basal ganglia, and cerebellum	Smaller GM and WM volumes in unmed vs. med or controls in all subdivided areas of the brain Male and female patients presented the same results Initial caudate nucleus difference (ADHD vs. NC) disappear over adolescence
Mostofsky et al 2002	12 ADHD males Age: 8–14 12 NC males Age: 8–14	Automated skull stripping, semi-automated segmentation based on fuzzy algorithm Total WM and GM volume of cerebral tissue Lobar WM and GM volume of separate left and right frontal, parietal, temporal, and occipital	In the frontal lobe WM and GM volumes were smaller compared with NC Left WM and right GM smaller compared with NC Prefrontal and premotor showed WM and GM reduction on both sides Smaller WM and GM volumes compared with NC Smaller total brain volume compared with NC
Overmeyer et al 2001	18 ADHD (3 females) Specific hyperkinetic; 1-year stimulant treatment prior to scan Age: 8–13 16 NC (1 female) Has sibling with ADHD Age: 7–14	Automated skull stripping thresholding and probability based segmentation Total brain volume Total GM and WM volumes	Greater reduction of WM on the left (8.2%) Left globus pallidus smaller in ADHD Significant GM volume reduction on the right side Reduction of total brain volume in ADHD (3.2%)
Filipek et al 1997	15 ADHD males ODD, conduct disorder, learning disability, depression and anxiety excluded Age: 9–16 15 NC males Age: 11–18	Segmentation based on semi-automated intensity contour mapping Precallosal (prefrontal), pericallosal (slices surrounding the corpus callosum divided into anterior and posterior), and retrocallosal (posterior parietal/occipital)	Smaller global WM in the group of nonresponders on both sides Significantly smaller retrocallosal (posterior parietal–occipital) WM volumes for nonresponders WM for responders were the same as NC Smaller total volume of anterior–superior frontal in ADHD, more on the right

ADHD, attention-deficit/hyperactivity disorder; NC, normal control subjects; GM, gray matter; WM, white matter; ODD, oppositional defiant disorder.

and because WM has an extremely high level of structural organization that compartmentalizes and restricts water motion. Diminished anisotropy of water diffusion has thus been proposed to reflect compromised WM integrity. Fractional anisotropy (FA) is a normalized measure of diffusion anisotropy that provides information about the degree of fiber organization and integrity, such that tissues with highly organized fibers oriented in the same direction (e.g., corpus callosum) would generally reflect higher FA. Fractional anisotropy yields values between 0 (i.e., isotropic or unrestricted diffusion, as in cerebrospinal fluid) and 1 (i.e., anisotropic or restricted diffusion due to barriers, as in organized WM fibers).

The goal of this preliminary study was to investigate WM integrity in children with ADHD relative to age- and gender-matched control subjects as inferred from DTI. We hypothesized that, relative to control subjects, children with ADHD would have lower WM FA in right-sided frontocortical and striatal regions, consistent with earlier anatomic MRI studies (Castellanos and Tannock 2002).

Methods and Materials

Participants

After a complete description of the study to the subjects and their parents, written assent and consent were obtained. This study was approved by the Institutional Review Board at the North Shore-Long Island Jewish Health System. Participation in this study did not interfere with ongoing treatment. Participants underwent an MRI scan, a diagnostic interview, administration of the parent version of the Conners' Attention

Deficit Scale (CADS) (Conners 1997), and a neuropsychological test battery. The battery consisted of eight subscales of the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler 1991), Block Design, Vocabulary, Picture Completion, Information, Coding, Similarities, Arithmetic, and Digit Span, to estimate full-scale intelligence quotient (IQ) scores (Donders 1997). The Wide Range Achievement Test-III (WRAT-III) (Wilkinson 1993) was administered as well. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield 1971), and socioeconomic status was measured with the Hollingshead system (Hollingshead 1975).

Psychiatric diagnoses were formed on the basis of structured interviews (Kiddie-Schedule for Affective Disorders, Present and Lifetime Version 1.0) (Kaufman et al 1996) of the children and their parents and chart review. The interviews were conducted by either a board-eligible child and adolescent psychiatrist (SLB) or a psychologist (JR) and were supervised by a board-certified child and adolescent psychiatrist (SK). Diagnosis of ADHD, combined type (314.01) was made on the basis of DSM-IV criteria (American Psychiatric Association 1994).

Eighteen ADHD patients were recruited from the child psychiatry, pediatric neurology, and developmental pediatrics section of the Schneider Children's Hospital in the Long Island Jewish Health System, New Hyde Park, New York. The inclusion criteria were: 1) current DSM-IV-defined diagnosis of ADHD combined type (314.01); 2) ratings of core ADHD symptoms reflecting difficulties in two settings relative to normative groups, ascertained by at least 2 SDs above age- and gender-specific means on both the Inattentive and Hy-

Table 2. Comorbid Diagnoses and Medication Information for Subjects with Attention-Deficit/Hyperactivity Disorder (ADHD) ($N = 18$)

Comorbid DSM-IV Diagnoses	
Oppositional defiant disorder (n)	2
Mathematics learning disorder (n)	1
Enuresis (n)	2
Adjustment disorder (n)	3
Psychopharmacologic Treatment for ADHD	
Stimulant treatment (n)	11
Nonstimulant treatment (n)	1
Combined stimulant and nonstimulant treatment (n)	1
Mean (SD) duration of treatment (mo)	19.47 (16.72)

perative-Impulsive subscales of the parent version of the CADS (Conners 1997); and 3) aged 7–11 years.

The exclusion criteria were: 1) WISC-III full-scale IQ < 70; 2) any previous psychotropic medication administration with the exception of stimulant treatment and/or atomoxetine; 3) evidence of neurologic or endocrine disorders on examination or by clinical history; 4) Tourette's disorder, or any other Axis I psychiatric disorder requiring treatment with medication; 5) any reading disability as determined by achievement tests (i.e., a 1.5-SD split between IQ and WRAT-3 reading scores); 6) any contraindications to MRI scanning (e.g., metal implants, pacemakers); 7) positive pregnancy test in female subjects; or 8) parental history of bipolar disorder or schizophrenia by self-report. Comorbid diagnoses and medication information of ADHD patients are presented in Table 2. As shown in the table, two patients presented with oppositional defiant disorder (313.81), one with a learning disorder (mathematics disorder, 315.1), two with enuresis (307.6), and three with adjustment disorder (309.9). None of the patients were receiving any medication for his or her comorbid diagnosis. We also chose to exclude children with ADHD, inattentive type (314.00) because evidence suggests that it is probably etiologically distinct (Neuman et al 1999), and thus, the inclusion of such subjects would reduce the power of the study.

Some of the children with ADHD were receiving stimulants ($n = 11$, including 4 receiving stimulants for less than 10 days), atomoxetine ($n = 1$), or a combined treatment of stimulant and nonstimulant medications ($n = 1$) at time of scanning. The remaining ADHD subjects were drug naïve ($n = 5$).

Table 3. Detailed Magnetic Resonance Imaging Parameters

Sequence Name	Purpose of Sequence	Orientation	TR/TE (msec)	Matrix	NEX	Thickness/Gap (mm)	FOV (cm) ²	Echo Trains Length	Imaging Time (min)
3 Plane Localizer	Initial localization	3 plane	N/A	256 × 128	2	5/2	24	N/A	0:24
Fast Spin Echo	Localize AC-PC	Sagittal	2000/68	256 × 192	1	3/0	22	12	0:30
Diffusion Tensor	Acquire $b = 0$, $b = 1000$ DTI	Paralleled to AC-PC	10,000/80	128 × 128	2	5/0	22	N/A	9:00
Double-Echo Fast Spin Echo	Unwarping, registration, and clinical	Paralleled to AC-PC	4000/17,102	256 × 256	2	5/0	22	16	3:20
3D IR-Prep SPGR	Registration, morphometry, and clinical	Coronal	10.1/4.2	256 × 192	1	1.5/0	22	N/A	7:59
FLAIR	Clinical	Paralleled to AC-PC	10,000/140	256 × 192	1	5.0/0	22	N/A	4:40

TR, repetition time; TE, echo time; NEX, number of excitations; FOV, field of view; N/A, not applicable; AC-PC, anterior commissure–posterior commissure; DTI, diffusion tensor imaging; 3D, Three dimensional; IR-Prep, inversion prep pulse; SPGR, spoiled gradient recalled; FLAIR, fluid-attenuated inversion recovery.

Fifteen control subjects were recruited through the Zucker-Hillside Hospital with advertisements in local newspapers, community fliers, and notices sent to churches, libraries, and local organizations. The exclusion criteria for control subjects, ascertained through a two-stage process that involved a telephone screening followed by an interview with the parent and child, were: 1) an Axis I disorder; 2) history of reading disorders; 3) WISC-III full-scale IQ < 70; or 4) ongoing medical or psychiatric disorders. We also excluded control subjects with a parental history of a significant Axis I disorder.

MRI Procedures

Magnetic resonance examinations were conducted at the Long Island Jewish Medical Center on a 1.5-T GE Neuro Vascular Interactive (NV/i) system (GE Healthcare, Waukesha, Wisconsin). This unit is equipped with high strength (50 mT/m) and a high-speed gradient system (slew rate = 150 T/m/sec) capable of conducting DTI procedures. All scans were carried out and monitored by the principal investigator (MA) and reviewed by a neuroradiologist for clinical evaluation. Scans with motion artifacts were repeated. We minimized movement by stabilizing the head with cushions and tape before scanning. One patient received 25 mg of diphenhydramine orally before the scan. In some cases, magnetic resonance-compatible video goggles were used to show movies to children during the scan to enhance compliance with the procedure.

In addition to the acquisition of routine clinical scans (T1, T2, and fluid-attenuated inversion recovery) to rule out any incidental pathologic abnormalities, DTI with matching fast spin echo double echo sequence for segmentation and three-dimensional spoiled gradient recalled (SPGR) with inversion prep pulse were obtained. Additional sagittal slices were acquired to determine the anterior commissure–posterior commissure (AC-PC) orientation. Scan orientations for all sequences, except the three-dimensional, were parallel to the AC-PC plane. The details of all sequence parameters are depicted in Table 3.

The diffusion tensor sequence used in this study has a total of 25 diffusion gradient directions for acquisition of 23 slices through the whole brain. Diffusion gradients applied along the non-collinear directions with $b = 1000$ s/mm² and number of excitations (NEX) = 2 and a T2 volume without diffusion weighting ($b = 0$; NEX = 2). None of the diffusion gradients were

repeated or inverted. Images were acquired parallel to the AC-PC with a ramp sampled spin-echo, single shot echo planar imaging method. We did not find any evidence for high frequency or Nyquist ghost on the diffusion images as determined from a quantitative in-house quality control program and from visual inspection of images at the time of scans. An FA map was computed from the 26 DTI volumes for each subject after derivation of the eigenvalues of the diffusion tensor matrix for each voxel with methods described by Basser (1995) and Basser and Pierpaoli (1998).

Image Processing

The key to a successful voxelwise analysis is the application of a reliable inter- and intrasubject registration. The intrasubject registration consisted of four essential image analysis steps: 1) skull stripping, which separates brain from nonbrain tissue; 2) distortion correction, which corrects for echo planar distortion correction; 3) rigid body registration, which corrects head motion during the scan and registers two differently acquired images into one to provide comparable images in the same orientation with the same dimension; and 4) image segmentation, which separates images of white, gray, and cerebrospinal fluid. In this analysis, we used the WM image of subjects to correct for WM of FA images.

The intersubject registration was performed to co-register all images to common Talairach space. According to the three-dimensional SPGR T1-weighted images, the subject with median brain volume was selected as the template image and was then transformed into Talairach space. Subsequently, all other subjects were registered to this Talairach template.

Intra- and intersubject registrations produce transformation matrices or warp fields that are specific to each subject. One resultant transformation was then applied to the original FA map by a single interpolation operation. This approach might reduce potential interpolation errors because only a single operation is applied to the FA maps, representing the combination of all registrations and distortion corrections. Thus, we obtained 33 FA maps (18 patients and 15 healthy volunteers) of matrix size $161 \times 191 \times 151$ and voxel size $1 \times 1 \times 1 \text{ mm}^3$ in common Talairach space. The following is a short description of the processes.

Skull Stripping. Three-dimensional SPGR images were edited to delete nonbrain regions with the MEDx (Sensor Systems, Sterling, Virginia) and FSL-BET (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, United Kingdom) software packages and for computation of total intracranial volume for each subject.

Rigid Body Registration. For intrasubject registration, the cropped SPGR volume was registered to the double echo spin echo T2/proton density (PD) volumes for each individual subject with an in-house program (Ardekani 2005). This resulted in a resliced SPGR volume with the same orientation and voxel dimension as the T2/PD volumes. The resliced SPGR volume was used as a mask to delete nonbrain regions from the T2 and PD volumes.

Distortion Correction. To correct for the spatial distortion of the DTI echo planar imaging data, the $b = 0$ DTI volume was registered to the cropped T2 volume with an in-house nonlinear registration program (Ardekani et al 1995). Figure 1 shows the degree of distortion correction in a slice from the original and distortion-corrected $b = 0$ images.

Segmentation. A segmentation process was carried out with FSL-FAST tissue segmentation from the shareware program of the Oxford Centre for Functional Magnetic Resonance Imaging of the

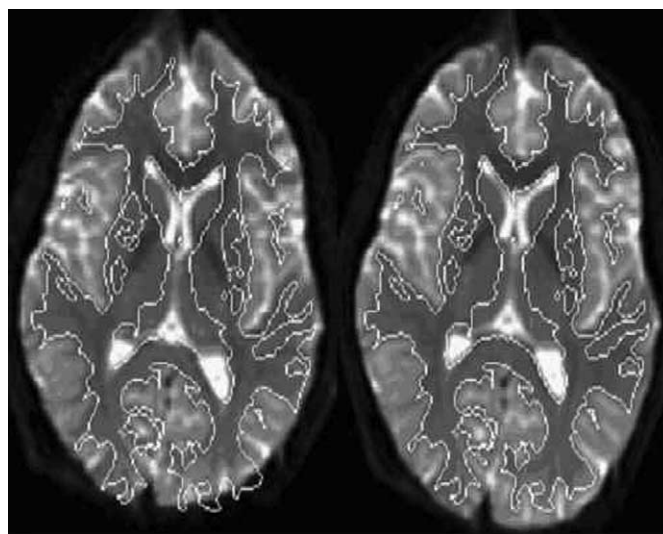


Figure 1. White matter boundaries superimposed on an original T2 image (b₀) of the diffusion tensor imaging (left) and on the distortion-corrected diffusion slice (right). Note the distortion in the posterior occipital region that has been corrected.

Brain (Image Analysis Group 2004). The resulting image sets (i.e., cropped T2/PD and T1 axial from resliced SPGR) were used as three channels in the FSL-FAST program to obtain WM, gray matter, and cerebrospinal fluid images. The WM image of these segmentations was used to correct the WM components of FA images.

White Matter Correction

To perform WM correction, the nonlinear transformation to Talairach space was also applied to individuals' WM images. Although the voxel intensities for the WM images were initially binary (i.e., WM present or absent), after this nonlinear interpolation the intensities had a distributed spectrum between 0 and 1. An average WM mask was then used to minimize low signal-to-noise voxels and voxels within the cerebrospinal fluid and grey matter; the threshold for this mask was set at 40% of the mean image intensity, as in our previous study (Szeszko et al, in press). Thus, only voxels that exceeded this intensity threshold were included in the analysis. Both the registered FA and WM images were smoothed with a three-dimensional isotropic Gaussian kernel of 3 mm.

Statistical Analyses

Group differences in demographic variables were examined with independent-samples t tests and/or χ^2 tests.

To control for potential partial volume effects in our analysis, FA values for each voxel were adjusted for WM intensity through linear regression. Two-sample t tests were performed at each voxel on the corrected FA values between patients and control subjects. Voxels that had a t statistic greater than 3.85 ($p < .01$) and were part of a spatially contiguous cluster size of 200 voxels or greater were considered to have significantly different FA in patients compared with healthy volunteers.

Results

Patients and comparison subjects did not differ significantly in distributions of age, handedness, parental social class, height, or full-scale IQ or subtests scores. Patients with ADHD were lower

Table 4. Patient and Control Subject Demographics

Characteristic	ADHD Group	<i>n</i>	Control Group	<i>n</i>	Fisher's Exact Test
Gender (Male:Female)	12:6	18	9:6	15	.731
Handedness (Right:Left) ^a	18:0	18	12:3	15	.083
Parent SES (Low:High) ^b	7:11	18	4:11	15	.712
Age (y)	8.94 (1.5)	18	9.13 (1.4)	15	<i>t</i> = .368, <i>p</i> = .715
Height (cm)	138.43 (10.5)	18	139.95 (8.6)	15	<i>t</i> = .450, <i>p</i> = .656
Weight (kg)	30.65 (7.0)	18	38.39 (14.2)	15	<i>t</i> = 2.043, <i>p</i> = .050
Conners' Total ^c	81.61 (4.26)	18	43.40 (3.89)	15	<i>t</i> = -26.69, <i>p</i> = .000 ^d
Conners' Inattentive Subscale	79.28 (5.29)	18	43.93 (4.67)	15	<i>t</i> = -20.148, <i>p</i> = .000 ^d
Conners' Hyperactive Impulse Subscale	79.50 (6.97)	18	44.00 (2.39)	15	<i>t</i> = -18.80, <i>p</i> = .000 ^d
WISC-R Full Scale IQ ^e	101.89 (20.9)	18	105.07 (10.0)	15	<i>t</i> = .540, <i>p</i> = .593
WISC-R Vocabulary	10.56 (4.4)	18	11.93 (2.7)	15	<i>t</i> = 1.052, <i>p</i> = .301
WISC-R Block Design	10.22 (4.4)	18	10.33 (3.5)	15	<i>t</i> = .080, <i>p</i> = .937
WRAT Reading ^f	107.81 (14.6)	16	107.57 (12.7)	14	<i>t</i> = -.048, <i>p</i> = .962
WRAT pseudoword decoding ^f	108.31 (7.5)	13	102.00 (10.4)	11	<i>t</i> = -1.723, <i>p</i> = .099

Data are presented as *n* or mean (SD). SES, socioeconomic status.

^aEdinburgh Handedness Scale (Oldfield 1971).

^bHollingshead Scale (low = 4, 5 and high = 1,2,3; Hollingshead 1975).

^cConners' Attention Deficit Scale-Parent (Conners 1997).

^d*p* < .01.

^eThe Wechsler Intelligence Scale for Children-III (Wechsler 1991).

^fWide Range Achievement Test (Wilkinson 1993).

in average body weight, and the groups differed significantly on all Conners' scores (see Table 4).

Clusters of significant voxels were superimposed on the average normalized SPGR image of all 33 subjects, as illustrated in Figures 2 and 3. A significant decrease in FA was observed in three regions on the right (Figure 2) and three regions on the left (Figure 3) hemispheres in patients as compared with healthy volunteers. Figure 2 shows the regions in which FA was reduced: premotor (left column), anterior limb of internal capsule or fronto-cortico-striatal (middle column), and cerebral peduncle (right column). Figure 3 shows significantly reduced FA at the level of middle cerebellar peduncle (Brachium pontis) exiting pons on the left side (left column) that enters the cerebellum (middle column) and the left parieto-occipital region (right column). A summary of the significant clusters (200 contiguous voxels, *p* < .01) with their Talairach coordinates is presented in Table 5.

To explore whether the finding presented in the middle column of Figure 2 reflects the frontostriatal region, the threshold was relaxed to see how the decreased FA spread. Figure 4 shows the decreased FA of the frontal striatal region at a more relaxed threshold (200 contiguous voxels, *p* < .05); the decreased FA region extended throughout the anterior limb of the internal capsule in the region of the striatum.

An exploratory analysis was conducted to estimate the effect of medication treatment on the DTI findings. We conducted direct group comparisons of medicated (*n* = 13) versus drug naïve (*n* = 5) subjects of FA values across all six brain regions where we found decreased FA in patients. We found no significant group differences (*p* < .10).

Post hoc exploratory analyses revealed a significant negative relationship between patient's score on the Conners' Inattentive Subscale and FA in the cerebellum (*r* = -.50, *p* = .40). All other correlational analyses between symptom measures and FA values in the 6 regions were statistically nonsignificant.

Discussion

To our knowledge, this report represents the first DTI study in children with ADHD. This study showed decreased FA in the right supplementary motor area, right anterior limb of internal capsule, right cerebral peduncle, left middle-cerebellar peduncle, and left cerebellum in children with ADHD compared with

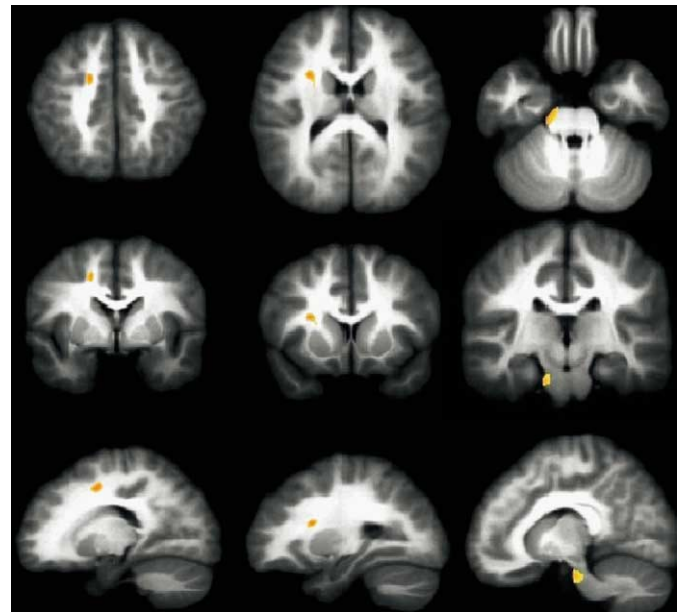


Figure 2. Right hemispheric areas of significant decreased fractional anisotropy in children with attention-deficit/hyperactivity disorder as compared with age- and gender-matched control subjects. Patients showed decrease in areas of premotor (left column), anterior limb of internal capsule (fronto-striatal) region (middle column), and the right cerebral peduncle (right column).

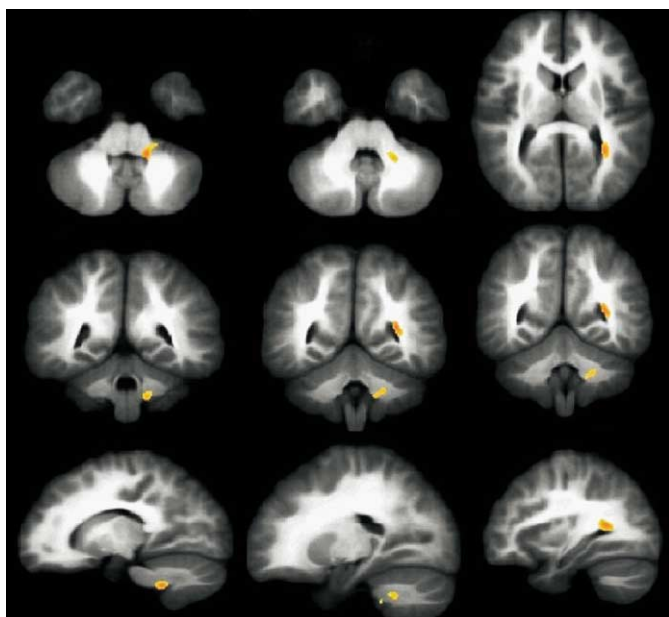


Figure 3. Left hemispheric areas of significant decreased fractional anisotropy (FA) in children with attention-deficit/hyperactivity disorder (ADHD) as compared with age- and gender-matched control subjects. Decreased FA in ADHD patients is shown for left middle cerebellar peduncle (left column), left cerebellum (middle column), and left parieto-occipital area (right column).

control subjects. These findings are consistent with previously reported MRI studies in ADHD that found abnormalities in the right hemisphere and cerebellum (Durston et al 2003; Giedd et al 1999).

The finding of lower FA in children with ADHD is intriguing given the role of the supplementary motor area in planning, initiation, and execution of motor acts (Amador and Fried 2004; Passingham 1993). Furthermore, the greatest reductions in glucose metabolism in adults with childhood-onset hyperactivity were found in the premotor cortex and the superior prefrontal cortex (Zametkin et al 1990). Additional literature also suggests that deficits in motor inhibition processes are associated with ADHD, combined type (Barkley 1997; Tannock 1998). Together, these data implicate a neurodevelopmental process that alters neural system configuration, particularly in the motor circuit of the right hemisphere in children with ADHD.

Although the functional implications of structural abnormalities in WM of the right frontostriatal region remain unclear, the development of right frontostriatal circuitry is thought to be important in the development of organization and planning



Figure 4. A more relaxed threshold of 200 contiguous voxels ($p < .05$) shows the spread and extent of decreased fractional anisotropy in the frontostriatal region.

capacities (Alexander et al 1986; Goldman-Rakic 1987). Casey et al (1997) have found that poorer performance on response inhibition tasks correlated predominantly with reduced right caudate and prefrontal volumes in 26 male children with ADHD. Similarly, Semrud-Clikeman et al (2000) reported that poorer performance on a task of sustained attention was related to smaller volume of the right anterior superior frontal WM. These anatomic findings are also consistent with preliminary findings from functional MRI studies. Durston et al (2003) used a cognitive control task in an MRI study that showed that children with ADHD do not activate frontostriatal regions in the same manner as normally developing children. They concluded that there is a relative lack of or delay in the maturation of ventral frontostriatal circuitry.

In addition to the hypothesized right-sided findings in both frontal and striatal regions, the reduction of FA in the WM of the right cerebral peduncle and the left cerebellum also is of interest. Prior volumetric MRI studies have reported anatomic abnormalities in the cerebellum of children with ADHD (Berquin et al 1998; Castellanos et al 1996, 2002; Mostofsky et al 2002). Clinical studies of children with cerebellar lesions (Levisohn et al 2000) show impairments in higher functions, such as executive tasks, including planning and sequencing, visual-spatial function, expressive language, verbal memory, and modulation of affect. We conducted exploratory analyses to examine the effects of severity of ADHD symptoms with deficits in FA in children with ADHD. We found that decreased FA values in the cerebellar region in children with ADHD (Figure 3, middle column) were associated with increased severity of inattentive subscale scores of the CADS (Conners 1997). These results support that the cerebellum plays a greater role in ADHD patients and their symptoms than was previously indicated in earlier studies (Castellanos et al 2002; Durston et al 2003; Giedd et al 1999).

There is now substantial and detailed evidence documenting a link between the cerebellum and higher order functions through the corticopontocerebellar circuit (Allen and Tsukuhara 1974; Brodal 1978; Levisohn et al 2000; Schmahmann 2004; Schmahmann and Pandya 1997; Schmahmann and Sherman

Table 5. Significant Clusters Identified with Decreased Fractional Anisotropy in Children with Attention-Deficit/Hyperactivity Disorder as Compared with Normal Control Subjects

Cluster	Anatomic Definition	No. of Contiguous Voxels	Talairach Coordinates		
			x	y	z
1	Right premotor (supplementary motor cortex)	218	18	1	41
2	Right anterior limb of internal capsule (frontostriatal)	238	25	10	18
3	Right cerebral peduncle (right pons)	298	13	-21	-20
4	Middle cerebellar peduncle (left pons)	220	-21	-49	-27
5	Left cerebellum (anterior lobe)	214	-14	-43	-32
6	Left parieto-occipital region	391	-31	-48	12

1998). The course of corticopontocerebellar fiber pathway has been thoroughly studied in the rhesus monkey (Kelly and Strick 2003; Schmahmann 1977, 2004; Strick 2002). This fiber pathway consists of a feedforward and a feedback limb. The feedforward limb is composed of the corticopontine and pontocerebellar fiber projection, which carries associative, paralimbic, sensory, and motor information from the cerebral cortex to the pons. The feedback loop consists of the cerebellothalamic and thalamocortical pathways (Dum and Strick 2002, 2003; Kelly and Strick 2003; Picard and Strick 2003; Schmahmann 1977; Strick 2002).

The feedforward limb of the corticopontocerebellar circuit terminates in multiple areas of the pons (Schmahmann et al 2004); however, little is known about the projection of fibers from the pons to the cerebellum (Schmahmann, personal communication, October 11, 2004). As depicted in Figure 2, the three right areas of decreased FA are at the level of the supplementary motor area (left column), the anterior limb of internal capsule (middle column), and the cerebral peduncle of the pons (right column), suggesting involvement of the feedforward limb of the corticopontocerebellar circuit in children with ADHD.

As shown in Figure 3, the left area of decreased FA at the level of the middle cerebellar peduncle (left column) might represent the point of entry of these fibers into the cerebellum after decussating in the pons. The second area of decreased FA on the left side is at the level of dentate nucleus of the cerebellum (middle column), which might be involved in the feedback loop of the corticopontocerebellar circuit (Dum and Strick 2003; Kelly and Strick 2003). The dentate nucleus of the cerebellum is believed to be involved in motor and nonmotor functions of the rhesus monkey, and it is thought to play a role in short-term working memory, rule-based learning, and higher order planning (Dum and Strick 2003). Application of tractography, however, is needed to graphically track the course of fibers through the areas of decreased FA to establish whether a connection exists among these areas and whether they follow the feedforward and feedback limb of the corticopontocerebellar circuit.

Overall, the study supports WM pathology in patients with ADHD examined early in the course of illness with DTI. Our results show that, in addition to the frontostriatal area, the cerebellum also plays an important role in the pathophysiology of ADHD. Several limitations to our study preclude firm conclusions. Because the sample size was small, we had limited power to examine the effects of age, IQ, sex, and severity of ADHD symptoms on FA measures. Also, we used a clinically referred sample; thus, these findings might not be generalizable to all patients with ADHD. In addition, a possible limitation of voxel-wise analysis is the problem of multiple comparisons and the increased risk of a type I error. To limit this problem, we used a conservative cluster size to examine differences between patients and control subjects of more than 200 voxels at a statistical threshold of $p < .01$, similar to what has been reported in prior DTI studies (Ardekani 2005; Hubl et al 2004).

Another confounding factor is that a significant proportion of the subjects included in this sample had received prior psychotropic medications. The effects of stimulant medications on diffusion measures are unknown; however, there is some evidence that stimulant medications might normalize anatomic deficits in WM in children with ADHD (Castellanos et al 2002). We did not find any differences, even at a trend level ($p < .10$), between patients who were drug naïve and patients who had received prior medication. These data must be interpreted with caution, because of the small sample size, the cross-sectional nature of this study, and the fact that these analyses had limited

power to detect a medication effect. Also, we did not systematically assess parental history for the presence of psychiatric disorders in first-degree relatives of our ADHD subjects and control subjects. This could have potentially biased our findings because of inclusion of healthy control subjects with a family history of ADHD.

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