Published in final edited form as:

J Child Neurol. 2011 October ; 26(10): 1296–1302. doi:10.1177/0883073811405662.

Increased Regional Fractional Anisotropy in Highly Screened Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract

Diffusion tensor imaging data were collected at 3.0 Tesla from 16 children with attention-deficit hyperactivity disorder (ADHD) and 16 typically developing controls, ages 9 to 14 years. Fractional anisotropy images were calculated and normalized by linear transformation. Voxel-wise and atlas-based region-of-interest analyses were performed. Using voxel-wise analysis, fractional anisotropy was found to be significantly increased in the attention-deficit hyperactivity disorder group in the right superior frontal gyrus and posterior thalamic radiation, and left dorsal posterior cingulate gyrus, lingual gyrus, and parahippocampal gyrus. No regions showed significantly decreased fractional anisotropy in attention-deficit hyperactivity disorder. Region-of-interest analysis revealed increased fractional anisotropy in the left sagittal stratum, that is, white matter that connects the temporal lobe to distant cortical regions. Only fractional anisotropy in the left sagittal stratum was significantly associated with attention-deficit hyperactivity disorder symptom severity. Several recent studies have reported pathological increases in fractional anisotropy in other conditions, highlighting the relevance of diffusion tensor imaging in identifying atypical white matter structure associated with neurodevelopmental processes.

Keywords

attention-deficit hyperactivity disorder (ADHD); development; cognitive; diffusion tensor imaging; magnetic resonance imaging (MRI)

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Author Contributions

EMM, LEC, SLR, WEK, and MBD participated in the design of the study, writing of protocol, and interpretation of results; DJP and MR participated in the design of the study, writing of protocol, recruitment of patients, coordination of other clinical investigators, and interpretation of results. All authors have written or reviewed the manuscript for intellectual content.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved by the Johns Hopkins Medicine Institutional Review Board. All participants signed informed consent forms prior to participation.

Much is known from structural imaging about the cortical maturation in children with attention-deficit hyperactivity disorder (ADHD), compared to typically developing children^{1–4}; however, less is known about developmental abnormalities in the underlying white matter. White matter anomalies have been observed in children with ADHD using anatomical magnetic resonance imaging^{5–8} and may contribute to critical functional deficits related to processing speed^{9,10} and motor dysfunction.¹¹

Diffusion tensor imaging is an imaging method that has been used to evaluate white matter organization through the measurement of the diffusion of water within white matter regions and tracts, providing information on the subvoxel microstructure. Fractional anisotropy is a derived measure that reflects directionality of water diffusion through tissue, thus providing an indication of white matter integrity. Anomalous development of components of white matter bundles, particularly axons, can lead to a reduction in fractional anisotropy, reflecting less directed diffusion.¹²

Despite the considerable interest in both ADHD and diffusion tensor imaging research, there have been very few studies to date that have used diffusion tensor imaging to probe microstructural abnormalities that may be related to the functional deficits observed in individuals with ADHD. Of these studies, the majority have found fractional anisotropy decreases in varying regions. For example, using voxel-wise analyses to study children with ADHD (hyperactive-impulsive and combined subtypes only), Ashtari et al¹³ found that children with ADHD (12 boys, 6 girls) had decreased fractional anisotropy values in right supplementary motor area, right striatum, bilateral cerebellar peduncle, and left cerebellum. The results are consistent with recent findings highlighting decreased supplementary motor area white matter volumes in children with ADHD,¹⁴ as well as prior behavioral research implicating the role of the supplementary motor area in motor response preparation.^{15,16} In a sample of only boys with ADHD, Hamilton et al¹⁷ also found reduced fractional anisotropy in the corticospinal tract and superior longitudinal fasciculus, suggesting that motor and attentional networks may be selectively disrupted in boys with ADHD—especially those with a high degree of comorbidity. Similarly, Casey et al¹⁸ found decreased prefrontal fractional anisotropy to be significantly correlated with performance on a computerized go/no-go test in children with ADHD. In addition, a region-of-interest-based study by Makris et al¹⁹ focused exclusively on the fractional anisotropy of the cingulum bundle and the superior longitudinal fasciculus of adults who had been diagnosed with ADHD as children. They found fractional anisotropy decreases in both tracts restricted to the right hemisphere. Aside from this study, all 3 of the other studies that identified reduced fractional anisotropy in ADHD had samples that included multiple comorbid conditions, for example, learning disabilities. More recently, Pavuluri et al²⁰ reported reduced fractional anisotropy in 13 children with ADHD (12 boys) compared with 15 controls (6 boys) in the anterior limb and superior regions of the internal capsule; however, the findings may have been driven, in part, by the imbalance in sex distribution between the 2 groups. Furthermore, it was unclear how the children in this study were screened for learning disabilities, which may have contributed to white matter anomalies.

In contrast, Silk et al²¹ recently identified increased fractional anisotropy in frontotemporal and parietal-occipital regions among children with ADHD—combined type (screened for comorbidities, including learning disabilities). Similarly, in a recent study from China, Li et al²² found increased fractional anisotropy in right frontal white matter among children with ADHD. It may be that among uncomplicated ADHD, there may be diminished axonal branching and/or increased axonal packing, which may drive the increase in fractional anisotropy. This interpretation would be consistent with prior functional imaging findings of hypo-activation in regions important for response preparation, processing speed, attention, and motor control.^{23,24} Two very recent reports^{25,26} also identified both fractional

anisotropy increases and decreases in voxel-wise comparisons between individuals with ADHD and controls. In both studies, reduced branching and crossing were suggested as a possible explanation of pathologically related fractional anisotropy increase, although it was not clear from either study whether the samples were screened for learning disabilities.

The present investigation examined the neural correlates of ADHD in a highly screened and balanced cohort, with diffusion tensor imaging data collected at 3.0 Tesla, using both voxel-wise and atlas-based region-of-interest analyses.

Methods and Materials

Participants

Participants were recruited as part of a study examining the brain mechanisms in ADHD and reading. The study was approved by the Johns Hopkins Medicine Institutional Review Board, and all participants and parents signed an approved consent to participate. Children included in the study were between 9 and 14 years and had full-scale IQ scores of 80 or higher, based on the Wechsler Intelligence Scale for Children (4th ed).²⁷ Exclusion criteria included a history of speech/language disorder or basic word recognition difficulties, evidence of visual or hearing impairment, or history of other neurological or significant psychiatric disorder. Children with ADHD who were taking stimulant medication were removed from the medication on the day of and day prior to cognitive testing. Children with ADHD taking psychotropic medications other than stimulants were excluded. A total of 32 children (16 controls, 16 ADHD) were included in the present analyses.

Participants were screened for psychiatric diagnoses using a structured parent interview (Diagnostic Interview for Children and Adolescents, 4th ed).²⁸ In addition, ADHD-specific and broad behavior rating scales (Conners' Parent Rating Scale–Revised, long form/Conners' Teacher Rating Scale–Revised, long form,²⁹ ADHD Rating Scale–IV³⁰) were used to confirm ADHD diagnosis. Children with diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed) other than oppositional defiant disorder and specific phobias were excluded from both groups. All participants were also screened for basic word reading difficulties, which were defined as a score less than the 25th percentile on the Basic Reading Composite of the Woodcock Johnson–III Tests of Achievement.³¹

In addition to the entry criteria above, children were included in the control group if they had *T* scores ≥ 60 on the ADHD (inattentive; hyperactive/impulsive) subscales of Conners' Parent Rating Scales–Revised or Conners' Teacher Rating Scales–Revised and ratings of 2 or 3 on 3 or fewer items from the inattention or hyperactivity/impulsivity scales of the Home or School Form of the ADHD Rating Scale–IV. Additional exclusionary criteria for the control group included any history of mental health services for behavior or emotional problems, parent or teacher report of previous history of academic problems requiring school-based intervention services, or history of defined primary reading or language-based learning disability. Children were included in the ADHD group based on diagnosis of ADHD (any subtype) based on the Diagnostic Interview for Children–IV and *T* scores ≥ 65 on the ADHD (inattention; hyperactive/impulsive) subscales of Conners' Parent or Teacher Rating Scales and ratings of 2 or 3 on 6 or more items from the inattention or hyperactivity/impulsivity scales of the Home or School Form of the ADHD Rating Scale–IV.

Image Acquisition

Diffusion tensor imaging was performed using single-shot echo-planar imaging with multicoil sensitivity-enhanced acquisition (reduction factor of 2.5) on a 3.0 Tesla Philips Gyroscan NT scanner. Slices of 2.5 mm with no gap were collected to cover the entire cerebrum and brainstem (echo time, 86 milliseconds; repetition time, 3 seconds). The

acquisition matrix was 96×96 , reconstructed to 256×256 with a field of view of 240×240 mm for a 0.94-mm isotropic in-plane resolution. Two runs were performed in each participant. Each run consisted of a single least diffusion-weighted image, and 32 images with diffusion weighting along spherically distributed directions were acquired with a b-value of 800 gauss/cm. Detailed descriptions about the protocol are available in other studies.^{32,33}

Diffusion Tensor Imaging Processing

Both runs in each subject were combined into a single data set and processed using an automated batch-processing program.³⁴ The gradient tables were adjusted according to the coregistration parameters.³⁵ To reduce the impact of imaging artifacts, the diffusion tensor was estimated with a method that identifies and excludes outliers to the tensor fit,³⁶ as implemented by the Camino diffusion toolkit.³⁷

Voxel-wise Analyses

The fractional anisotropy map for each subject was normalized into Montreal Neurological Institute standard space at 2-mm isotropic resolution by affine registration of the mean diffusion-weighted image to the Johns Hopkins University diffusion-weighted image template.³⁸ Normalized images were then smoothed with an 8-mm Gaussian kernel. Group comparisons and correlations with behavioral measures were performed with the second version of the University College of London's statistical parametric mapping software. Atlas assignments were obtained from the Talairach Daemon Atlas,³⁹ except where otherwise noted. Statistical parametric maps were computed at a threshold of $P < .001$ uncorrected, excluding clusters with a spatial extent of less than 10 voxels (80 mm^3).

Atlas-Based Region-of-Interest Analyses

Regions of interest drawn from the Johns Hopkins University White Matter Atlas were applied to the normalized, unsmoothed fractional anisotropy images. Thirteen atlas regions (both hemispheres where appropriate) were used: the body, splenium, and genu of the corpus callosum; the anterior and posterior corona radiata; the superior longitudinal fasciculus; the sagittal stratum; the anterior and posterior limb of the internal capsule; the cingulum; and the superior fronto-occipital fasciculus. These regions were chosen for their possible relevance to the functional deficits observed in ADHD, informed by the aforementioned publications and hypothesized structure-function relationships.⁴⁰ In addition, the middle cerebellar peduncle and the fornix were also included in the region-of-interest analysis as "negative control" regions, as group differences in fractional anisotropy would not be expected in those regions. Voxels with fractional anisotropy values less than 0.2 were excluded from the region-of-interest analysis to reduce misalignment error.

Brain/Behavior Correlations

The correlations between fractional anisotropy values from the region-of-interest analyses and total scores from the ADHD Rating Scale–IV Home Version were examined across diagnostic groups.

Results

Demographic and Clinical Data

Descriptive statistics for the sample are shown in Table 1. Of the 32 participants (16 children with ADHD and 16 controls), 84% were white, 12% African American, 2% Asian, 1% Hispanic, and 1% of mixed race. The groups were matched for sex (11 boys and 5 girls in each group). Within the ADHD group, there were 7 children with inattentive subtype and

9 with combined subtype. Five children in the ADHD group had oppositional defiant disorder, whereas 1 had a specific phobia of thunderstorms. Participants ranged in age from 9 to 14 years (mean, 11.2 years). There were no significant differences between ADHD and control groups in age, socioeconomic status, handedness, or racial composition.

Diffusion Tensor Imaging Data

Voxel-wise fractional anisotropy differences between groups—Regions in which fractional anisotropy values were found to be significantly different between children with ADHD and controls are listed in Table 2. Fractional anisotropy was found to be significantly increased in the ADHD group compared to the control group, most principally in the right superior frontal gyrus. Other regions of significantly increased fractional anisotropy included the left cingulate gyrus, the left lingual gyrus, the left parahippocampal gyrus, and the right posterior thalamic radiation (as identified by the Johns Hopkins University Diffusion Tensor Imaging White Matter Atlas⁴¹ (Figure 2 and Table 2). There were no regions where fractional anisotropy was found to be significantly decreased in ADHD compared to controls.

Fractional anisotropy differences between groups in atlas-based regions of interest—A 2-tailed *t* test revealed a 4.2% increase in fractional anisotropy in ADHD in the left sagittal stratum ($P = .025$) (Figure 2). A trend-level increase was also observed in the right sagittal stratum, and post hoc test of bilateral sagittal stratum fractional anisotropy yielded a *P* value of .018. Fractional anisotropy was not significantly increased in the remaining regions. Furthermore, none of the selected regions of interest showed significantly decreased fractional anisotropy in ADHD compared to controls. In addition, as expected, there were no significant group differences in fractional anisotropy for the 2 “control” regions. The common (overlapping) regions of significant increase obtained by region-of-interest analyses and voxel-wise analyses in the vicinity of the left sagittal stratum are also outlined in Figure 2. Within the sagittal stratum (which is lateral to the posterior thalamic radiation and adjacent to the junction of Brodmann areas 19, 39, and 37), there is an overlapping region of significant fractional anisotropy increase (obtained by both region-of-interest and voxel-wise methods) near the junction of the left parahippocampal gyrus (Brodmann area 19) and the left sagittal stratum (Figure 3).

Fractional anisotropy correlation with behavioral measures—Across groups, fractional anisotropy values from the left sagittal stratum were significantly (positively) associated with total ADHD symptom severity ($r = 0.375$; $P = .035$), such that greater fractional anisotropy values in this region were associated with a higher level of reported ADHD symptomatology. There were no significant associations between fractional anisotropy values obtained from any of the other atlas-based regions of interest and ADHD symptom severity.

Discussion

The current data suggest that among individuals with ADHD carefully screened for comorbidities (including conduct disorder, reading and language disorders, mood disorders, and most other psychiatric comorbidities), fractional anisotropy values can be increased, relative to typically developing controls, with increases specifically associated with severity of ADHD symptomatology. Specifically, multifocal white matter anomalies in ADHD were identified in regions important for executive control of behavior and efficient processing and motor speed, with most consistent findings in regions involving the left sagittal stratum and parahippocampal gyrus. In this regard, the findings are highly consistent with prior research that has identified posterior temporal-parietal white matter anomalies in ADHD.^{13,42} In

particular, the Davenport study also reported fractional anisotropy increases in bilateral temporal white matter in ADHD. The sagittal stratum and a few of the regions identified in the voxel-wise analyses are part of the occipital-temporal projection system and convey fibers from the parietal, occipital, cingulate, and temporal regions to subcortical destinations in the thalamus and brain stem structures.⁴³ Prior diffusion tensor imaging research has also suggested that there may be direct connections from the extrastriate occipital cortex to anterior temporal structures (involving occipital branches related to visual association regions and anterior temporal branches related to the lateral temporal cortex, parahippocampal gyrus, and amygdala) that allow direct, rapid access of visual information to anterior temporal structures and from anterior temporal structures to the occipital lobe.⁴⁴ In the context of an individual child, rapid communication between brain regions associated with visual perception and those associated with memory formation and retrieval may facilitate rapid processing of visual information. Thus, atypical measures of white matter cohesion along the course of this pathway, as we have found in this study, suggest a possible biological correlate of the well-documented processing speed deficits seen in children with ADHD.

Previous studies showing reduced fractional anisotropy in ADHD were obtained in ADHD groups with multiple comorbidities (including reading disabilities)—and mainly at 1.5 Tesla. Recent studies, however, have identified pathological increases in fractional anisotropy associated with genetic disorders, for example, Williams syndrome,⁴⁵ as well as ADHD.²¹ Thus, considering prior reports of reduced white matter volume⁴⁷ in ADHD, along with observations of increased fractional anisotropy, anomalous white matter development in ADHD may be a function of either reduced branching of white matter tracts or reduced integrity in a population of smaller, crossing fibers perpendicular to the locally dominant fiber, thus resulting in increased net directional preference of water diffusion within the white matter. This finding may be particularly apparent among children with highly screened ADHD (ie, those screened for comorbidities, especially reading and language disorders). In diffusion tensor imaging studies of ADHD in which learning disabilities and language disorders are not screened, the findings of reduced fractional anisotropy may be attributable to the reading disorders, as other studies of children with reading difficulties, including ours, have consistently noted decreased fractional anisotropy.^{48–51} It is also possible that the different pattern of findings in the present study is due in part to the inclusion of nearly equal numbers of children in the ADHD group with inattentive ($n = 7$) as combined subtypes ($n = 9$). Indeed, a nonparametric exploratory analysis (Mann-Whitney U) of fractional anisotropy values in the sagittal stratum by ADHD subtype revealed significantly increased fractional anisotropy values (relative to controls) for the inattentive subtype ($P = .018$), whereas fractional anisotropy increases for the combined subtype (relative to controls) were not statistically significant ($P = .380$). These findings suggest that increased fractional anisotropy findings in sagittal stratum may be associated more directly with inattentive ADHD symptomatology than with hyperactive/impulsive symptomatology. Future investigations should thus address this association more directly in larger samples.

A unique aspect of the current study design is the strict diagnostic procedures for ADHD and the exclusion of many comorbidities that could confound the interpretation of results. Although these sampling procedures produce ADHD samples that are more pure diagnostically, they also tend to be associated with groups with slightly higher than average measured intelligence. As such, the present findings may be less specifically applicable to children with a wider range of comorbidities. In addition, the inability of standard diffusion tensor imaging to resolve multiple fiber directions is an established limitation⁵² that was unresolved when this study began but now has some partial solutions proposed in the literature.^{53,54} Unfortunately, these protocols require collection of many more diffusion

weighed images; thus, these new methods were not feasible to implement on the current data.

The present findings also leave several questions unanswered, and thus future research should determine whether fractional anisotropy increase is due to increased white matter integrity, decreased branching, or abnormalities of minor crossing tracts, for which acquisition of high angular resolution diffusion imaging data will be required. Collecting such a data set would open the door to modern multitensor models or nontensor models, such as diffusion spectrum imaging or q-ball imaging, but would require an approximately 2-fold increase in scanner time.⁵⁵ In addition, voxel-wise analysis is an extremely sensitive technique and is more suited to exploratory analyses than to confirmatory studies. A region-of-interest-based analysis of diffusion tensor imaging data, in native space, in ADHD focused on the identified regions from the voxel-wise analyses (as we have performed in children with dyslexia)⁴⁸ would complement the current study but would ideally be performed on data from a new cohort of children, to avoid the problem of non independent statistical analyses.

Conclusion

In summary, these data provide evidence of white matter anomalies among children ages 9 to 14 years with uncomplicated ADHD, which, in this age range, are most consistently notable in posterior occipital-temporal regions that may underlie both the severity of ADHD symptoms and the efficiency of important life skills such as reading.

Acknowledgments

The authors thank Marin Ranta and Rebecca B. Martin for assistance with data collection and to Lisa Ferenc, Deana Crocetti, and Moshin Javid for help with manuscript preparation. Portions of this manuscript were presented at the 38th annual North American meeting of the International Neuropsychological Society in Atlanta, Georgia, on February 12, 2009.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Supported by National Institutes of Health Grants P50 HD052121, R01 HD044073, and P30 HD24061, the Johns Hopkins University School of Medicine Institute for Clinical and Translational Research, an NIH/NCRR CTSA Program, UL1 RR025005.

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Figure 1.
Increased fractional anisotropy in children with attention-deficit hyperactivity disorder compared to controls from voxel-wise analysis.

Figure 2.

The Johns Hopkins University Diffusion Weighted Image Atlas sagittal stratum region of interest overlaid on the average fractional anisotropy image, with the region of increase from the voxel-wise analysis. There is an overlapping region of significant fractional anisotropy increase near the junction of the left parahippocampal gyrus (Brodmann area 19) and the left sagittal stratum. Figure appears in color online at jcn.sagepub.com

Figure 3.

Box plot of fractional anisotropy increase in the left sagittal stratum among participants with attention-deficit hyperactivity disorder, compared to control participants.

Table 1

Demographic and Behavioral Information

Variable	Control (n = 16)	ADHD (n = 16)	P	η^2
Age, y	11.15 (2.14)	11.28 (1.55)	.85	1.22×10^{-3}
Full-scale IQ	115 (10.28)	108 (14.03)	.133	7.62×10^{-2}
Processing speed index	101.13 (20.74)	98.50 (16.36)	.697	5.32×10^{-3}

ADHD, attention-deficit hyperactivity disorder. Full-scale IQ and processing speed index are from the Wechsler Intelligence Scale for Children (4th ed.); η^2 , effect size eta-squared; numbers in parentheses are SDs.

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Regions in Which Fractional Anisotropy Was Significantly Greater in Children With Attention-Deficit Hyperactivity Disorder Compared to Controls

Table 2

Cluster Size	Regions Included	BA	Side	MNI coordinates		
				x	y	z
78	Superior frontal gyrus	10	Right	24	58	0
77	Lingual gyrus ^a	18	Left	-20	-72	-2
51	Parahippocampal gyrus	19	Left	-34	-50	-8
45	Posterior thalamic radiation ^b	NA	Right	38	-46	8
45	Cingulate gyrus	31	Left	-18	-52	26
15	Postcentral gyrus	3	Left	-26	-32	46
14	Precentral gyrus ^a	4	Right	32	-34	58

BA, Brodmann area; MNI, coordinates in Montreal Neurological Institute stereotaxic space; NA, not applicable.

^aGray matter region; all others regions identified were white matter.

^bRegion assignment obtained using Johns Hopkins University White Matter Atlas.