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Altered White Matter Microstructure in Children with Attention Deficit/Hyperactivity Disorder

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Abstract

Objective—Identification of biomarkers is a priority for attention deficit/hyperactivity disorder (ADHD). Studies have documented macrostructural brain alterations in ADHD, but few have examined white matter microstructure, particularly in pre-adolescent children. Given dramatic white matter maturation across childhood, microstructural differences seen in adolescents and adults with ADHD may reflect compensatory restructuring, rather than early neurophenotypic markers of the disorder.

Method—Using Tract-Based Spatial Statistics, mean fractional anisotropy (FA) maps were created using diffusion tensor imaging. FA and mean diffusivity (MD), and associated axial and radial diffusivity, were compared between 16 children with ADHD and 20 healthy children (age 7-9 years).

Results—ADHD youth showed reduced FA in fronto-parietal, fronto-limbic, cerebellar, corona radiata and temporo-occipital white matter compared to controls. In addition, ADHD was associated with lower MD in the posterior limb of the internal capsule and fronto-parietal white matter, and greater MD in fronto-limbic white matter. Lower axial diffusion and/or higher radial diffusion were differentially observed for ADHD youth in earlier versus later maturing areas of group FA/MD difference.

Conclusions—This study suggests that, even prior to adolescence, ADHD represents a disorder of altered structural connectivity of the brain, characterized by distributed atypical white matter microstructure. Additionally, later maturing fronto-limbic pathways also were abnormal in children with ADHD, likely due to delayed or reduced myelination, a finding not previously demonstrated in the adolescent or adult stages of the disorder. These results suggest that disruptions in white matter microstructure may play a key role in the early pathophysiology of ADHD.

Keywords

ADHD; DTI; attention; white matter; MRI

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Introduction

The U.S. Centers for Disease Control (2006) report that 3%-7% of children suffer from attention deficit hyperactivity disorder (ADHD), resulting in substantial societal cost.[1] Existing treatment helps to contain symptoms, but does not cure or prevent the disorder. Thus, pursuit of neurobiological markers and mechanisms remains crucial. In that regard, much has been learned about macrostructural brain abnormalities in ADHD, with neuroimaging confirmation of reductions in white matter volume,[2-5] and atypical morphometry in numerous brain regions, including prefrontal and parietal cortex, cerebellum, basal ganglia, and limbic structures (for review, see [6]). Functional neuroimaging work has revealed atypical functional connectivity in the adolescent and adult ADHD brain (for review, see [7]), namely in distributed fronto-striatal-cerebellar and parietal brain networks.[8-10] In addition, task-related functional neuroimaging studies have demonstrated atypical frontoparietal, frontostriatal, and frontotemporal brain response during cognitive tasks involving attention, decision making, and other aspects of executive behavior, often accompanied by poorer task performance among individuals with ADHD (for review, see [11, 12]). Consistent with this picture, a range of cognitive functions are also related to ADHD, including alterations in executive functioning, vigilance, temporal information processing, working memory, and related regulatory measures,[13] as well as alterations in motivational networks in the brain.[14] Despite evidence for distributed structural and functional abnormalities in the ADHD brain, many of which are associated with impairments in cognition, the role of white matter microstructure in the disease remains unclear, particularly in the maturational period prior to adolescence.

Diffusion tensor imaging (DTI) is an MRI-based technique used to characterize white matter microstructure by exploiting diffusion characteristics of water molecules in the brain.[15] Mean diffusivity (MD) and fractional anisotropy (FA) are two DTI-derived quantitative indices that have been informative in studying brain development.[16] Higher FA values are thought to reflect greater directional coherence of diffusion in white matter and may indicate greater axonal integrity and organization, while MD values reflect an estimate of the magnitude of diffusion in white matter pathways.[15] Decomposition of MD/FA, into axial (diffusion parallel to the axon) and radial diffusivity (diffusion perpendicular to the axon), provide additional microstructural information. Reductions in axial diffusion reflects perturbed axonal integrity and extra-axonal space, and reductions in radial diffusion suggest increased myelination.[17]

Microstructural abnormalities in white matter may lead to a disturbance in communication between brain regions, ultimately resulting in disrupted functioning and perhaps explaining the importance of distributed brain abnormalities in the ADHD literature. While some white matter pathways are largely developed by late childhood, several remain in an active state of maturation well into adolescence, particularly in association and projection fibers to and from the prefrontal cortex.[18, 19] Importantly, these maturational processes may cloud the early developmental picture of ADHD, because interactions between the disease process and neuromaturation may change across the lifespan. In addition, given emerging evidence suggesting that white matter microstructure may be experience-dependent,[20] atypical white matter findings in adolescent or adult populations with ADHD may be the result of compensatory restructuring, and may not reflect the nature of early developmental markers of the disorder. It is therefore critical to evaluate children in the early stages of ADHD.

Indeed, findings from studies of adult ADHD do not entirely overlap with those in younger samples. At least eight studies have used DTI to examine ADHD.[21-28] Initial results, in primarily adolescent samples, varied but suggest distributed microstructural white matter abnormalities across the brain in ADHD. These include atypical FA values in the corpus

callosum,[22] and frontostriatal,[21, 27] cerebellar,[21] parieto-occipital,[21, 24, 29] temporo-occipital,[29] and corticospinal[24] white matter, as well as widespread MD abnormalities.[27] The two studies of adults showed reduced FA and greater MD in ADHD, limited to later-maturing prefrontal white matter, including the anterior cingulum,[25, 26] orbitofrontal white matter,[25] and anterior fronto-parietal white matter pathways.[26]

These studies suggest that white matter microstructure is atypical in ADHD, and that by adolescence, this alteration in white matter is widespread. However, these findings raise important questions. Most saliently, nearly all previous studies focused on individuals in adolescence or adulthood. The few studies that included pre-adolescent children also included adolescents,[21, 24, 27, 28] so it remains unclear whether the observed effects are primary in ADHD, or are a consequence of many years of having the disorder, perhaps reflecting the confluence of reorganization and continued development of the brain. If microstructural abnormalities can be confirmed in samples exclusively of younger children, their importance as biomarkers and their potential for eventual clinical translation will be markedly enhanced, because ADHD emerges early in development and is commonly identified by early school-age.[30] Based on DTI studies showing diffuse microstructural white matter abnormalities in ADHD,[21-28] as well as functional studies suggesting a disturbance in fronto-striatal-cerebellar and parietal connectivity, [8-10] we hypothesized that, in this pre-adolescent sample, we too would see microstructural abnormalities in long-range connective pathways, particularly fronto-parietal, frontostriatal, and temporo-occipital white matter. In addition, although not seen in previous adolescent and adult studies of ADHD, given the protracted maturation of fronto-limbic pathways,[19] we further hypothesized these to be abnormal in pre-adolescent children with ADHD. Given the documented role of these brain pathways in higher-order cognition, as well as findings of atypical brain response and associated behavior in these regions in ADHD,[11] we further hypothesized that differences in white matter microstructure in these regions would largely be associated with the inattentive symptoms of the disorder.

Method

Participants

Recruited participants included 40 right-handed children aged 7 to 9 years, 22 of whom met DSM-IV criteria for ADHD and 18 non-ADHD comparison youth; however, 4 children (2 per group) were excluded due to excessive motion during imaging, resulting in 20 ADHD and 16 control youth used for analyses. Families of both groups were recruited from an ongoing study of children with ADHD via county-wide mailings and public advertisements. Written informed consent/assent was obtained from all families. All study procedures were conducted in accordance with the local Institutional Review Board.

Identification

Families passed through a multi-gate screening process to establish diagnostic groupings. An initial screen excluded youth who were ineligible due to parent reported history of neurological disorder/insult or major medical conditions, prior diagnosis of mental retardation or autistic disorder, or psychotropic medications (other than stimulants). Next, parents and teachers of remaining eligible youth completed the ADHD Rating Scale (ADHD-RS)[31] and the Conners Rating Scale-3rd Edition (Conners-3).[32] A parent completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-E)[33] during which the full range of Axis I childhood disorders (plus sleep disorders) were assessed. Sample interviews were videotaped and checked for fidelity and inter-interviewer consistency (all $k > .80$). Children completed an assessment of IQ, consisting of a three-subtest short form

(Block Design, Vocabulary, and Information) of the WISC-IV.[34] Estimated Full Scale IQ of ≥75 was necessary for inclusion.

Final ADHD and Other Diagnoses

Final diagnosis was achieved by a best estimate procedure. All preceding clinical data were presented to a team, consisting of a child psychiatrist and clinical psychologist, who each independently arrived at a diagnosis for ADHD, as well as any comorbid disorders, using DSM-IV criteria. In addition to the exclusionary criteria noted above, youth were excluded for current depression or psychosis and current or past mania. Controls were also excluded for conduct disorder or learning disability. Diagnostic agreement rates were acceptable ($k > .80$) for all disorders observed. Disagreements were resolved by consensus. All ADHD subtypes were allowed.

Imaging Procedures

One week prior to scanning, children experienced a mock scanner to acclimate to the scanner environment and to train in lying still. Prior to the actual scan, children prescribed stimulant medication for ADHD ($n = 3$) underwent a 24-48 hour washout, with duration of washout determined by the type of preparation prescribed. Their exclusion did not alter DTI results, and thus, is not further discussed.

All children were scanned on a 3.0 Tesla Siemens Magnetom Tim Trio (Siemens Medical Solutions, Erlangen, Germany), with a twelve-channel head coil. Whole-brain, high-resolution T1-weighted anatomical imaging was acquired in the sagittal plane (TI = 900ms, Flip Angle = 10 degrees, TE = 3.58ms, TR = 2300ms, voxel dimensions = 1 mm × 1 mm × 1.1 mm slice thickness). Four sets of diffusion weighted images were collected using a 20-gradient direction, whole-brain echo-planar imaging (EPI) sequence, (TR = 9500ms, TE = 95ms, FOV= 240mm^2, b-value = 1000s/mm2, isotropic voxel dimensions = 2mm^3), and 3 images in which the b-value = 0 (total time: 15min, 4 sec). A static magnetic field map was also acquired, using the same parameters as the DTI sequence.

Image Processing

Using FSL's FMRIB Software,[35]datasets were corrected for eddy current distortion, intensity inhomogeneities, and head motion. FMRIB's Utility for Geometrically Unwarping EPIs was used to minimize distortions resulting from magnetic-susceptibility-induced local magnetic field gradients.[36] The DWI data were aligned using linear (affine) registration and Fourier interpolation using FMRIB's Linear Image Registration Tool. Affine aligned images were averaged and brain-extracted.[37] Although small motion correction was performed, we excluded participants with excessive movement as follows. An average root mean square (RMS) was determined based on the 6 motion parameters established by the co-registration of the images in which b=0. Youth with RMS values exceeding 2mm for ≥3 run registrations were excluded from analyses (control $n = 2$; ADHD $n = 2$), as noted earlier. Motion during scanning was not significantly different between groups ($t = -1.35$, $p = .19$).

DTI Quantification and Tract Based Spatial Statistics

Pre-processed images were used to derive FA and MD values for each voxel using AFNI's 3dDWItoDT.[38] Whole-brain voxelwise analyses of FA and MD were examined using FSL's Tract Based Spatial Statistics (TBSS) version 1.2.[39] First, a registration target image was selected and affine aligned to standard MNI152 space. Second, each subject's FA map was nonlinearly registered to the target using FMRIB's Non-linear Image Registration Tool (FNIRT) and resampled to a 1mm^3 voxel resolution.[40] Aligned FA images were averaged to create a group-wise mean FA map. Third, a white matter skeleton was created, representing

major tracts common across all subjects, and a mean FA threshold of >0.2 was applied to reduce partial volume effects.[39] This same threshold was applied to FA clusters of group difference, to remove outlying data likely due to partial voluming effects (n = 1 control participant for one FA cluster). Finally, each subject's aligned FA image was projected onto the white matter skeleton for subsequent voxelwise group-level statistics. In similar fashion, MD images were aligned to standardized space, and the nonlinear registration parameters, previously determined by FNIRT using FA maps, were applied to the MD maps. MD images were likewise merged and projected onto the FA derived white matter skeleton to perform statistical comparisons.

Data Analysis

To examine group differences in white matter microstructure, voxelwise ANCOVAs were performed on the FA/MD white matter skeleton, while covarying for gender, using AFNI's 3dttest+.[38] Both voxel probability and cluster size thresholding was used to correct for Type 1 error, as follows. Using Monte Carlo simulation with AFNI's AlphaSim program, 25 contiguous voxels exceeding a t-threshold of 2.73 (cluster volume ≥ 25 μL, voxelwise and clusterwise $\alpha < .01$; corrected *p*/voxel = 0.00000369) were required for cluster significance, assuming 1.8mm, 2.4mm, and 2.0mm (x, y, z) full width at half maximum intrinsic smoothing. To better understand group differences in FA/MD, extracted mean axial (λ_1) and radial ($(\lambda_2 + \lambda_3)/2$) diffusion values were examined via ANCOVA in SPSS, while controlling for gender, in each significant FA and MD cluster. Bonferroni correction was employed to determine statistical significance within FA and MD clusters ($p < .005$ for FA clusters; $p < .01$ for MD clusters).

To examine relationships between FA/MD values and ADHD symptoms, mean FA/MD values were extracted from significant between-group FA/MD clusters for each individual, and regression analyses were used to covary for gender and examine the relationship between FA/MD and each symptom dimension. Symptom dimensions were reflected by composite scores for inattention and hyperactivity-impulsivity by averaging z-scores for the Parent and Teacher's ADHD-RS and Conners-3 for each domain. Again, Bonferroni correction was employed to determine statistical significance ($p < .005$ for FA clusters; $p < .01$ for MD clusters).

Results

Demographics

See Table 1 for sample demographics and clinical summary. Groups did not differ with regard to age, IQ, ethnicity, or annual household income. Gender differed as so was statistically covaried in all analyses reported. Aside from the elevated rates of ODD in the ADHD group, which is nearly universal in such samples, active comorbid disorders were generally absent from the sample, with exception of two children with ADHD having generalized anxiety disorder (Table 1) and one child in each group with a history of a sleep disorder. Confirming diagnostic assignment, the ADHD group showed significantly greater inattentive and hyperactive-impulsive symptoms, as indexed by the Parent and Teacher reports for the Conners-3 and the ADHD-RS. Among the ADHD sample, 8 participants met diagnostic criteria for the inattentive-subtype, 1 for hyperactive-subtype, and 11 for combined subtype. In light of evidence that subtypes are not temporally stable,[41] we elected to include all subtypes in this analysis, deferring subtype comparisons to a later report with a larger sample.

Group Differences in Diffusion Characteristics

The ANCOVA of FA, controlling for gender, revealed significant group differences in 10 white matter clusters (Table 2 and Figure 1a). Mean differences in FA between groups remained significant for all clusters after covarying for presence of ODD in SPSS (all $p < .005$). Children with ADHD showed lower mean FA in bilateral fronto-limbic white matter (FA Clusters 1 and 2), bilateral temporo-occipital white matter (FA clusters 3 and 7), left cerebellar white matter (FA clusters 6 and 8), right fronto-parietal white matter (FA Cluster 9), right anterior and superior corona radiata (FA Clusters 4 and 10), and in the left posterior corona radiata (FA Clusters 5).

MD values revealed significant group differences in 4 white matter clusters (Table 2 and Figure 1b); all of which remained after covarying ODD (all $p < .005$). ADHD was associated with higher MD values in left fronto-limbic white matter (MD Clusters 1 and 3) and lower mean MD values in the right posterior limb of the internal capsule (MD Cluster 4) and superior longitudinal fasciculus (MD Cluster 2).

To better decipher the microstructural basis of these white matter abnormalities, mean axial diffusion, thought to reflect axonal characteristics, organization, and integrity,[15, 42] and mean radial diffusion, thought to reflect myelination,[17] were examined in each identified FA/MD cluster of group difference. Differences in FA and MD were due to a combination of differences in axial and radial diffusion between groups, most notably with FA/MD differences in later maturing fronto-limbic white matter[18, 19] (FA Cluster 1 and MD Clusters 1 and 3) driven primarily by increased radial diffusion in ADHD (Table 2).

White Matter Associations with ADHD Symptoms

With gender in the model, all clusters of FA/MD group difference were associated with inattention and hyperactivity symptoms ($p < .05$); however, after Bonferroni correction for multiple comparisons, FA in the left frontolimbic white matter (FA Cluster 1), right anterior corona radiata (FA Cluster 4), right frontoparietal white matter (FA Cluster 9), and right superior corona radiata (FA Cluster 10), as well as MD in the right superior longitudinal fasciculus (MD Cluster 2) remained significantly associated with both inattention and hyperactivity symptoms ($p < .005$). After correcting for multiple comparisons, FA in right frontolimbic white matter (FA Cluster 2), left posterior corona radiata (FA Cluster 5), and left temporo-occipital white matter (FA Cluster 7), as well as MD in left frontolimbic white matter (MD Cluster 1) and the right posterior limb of the internal capsule (MD Cluster 4) remained significantly associated only with symptoms of inattention ($p < .005$). With both symptom dimension simultaneously entered into the regression model, no clusters of group FA/MD difference remained significantly associated with either inattention or hyperactivity after correction for multiple comparisons.

Discussion

Evaluation of white matter microstructure in childhood ADHD is crucial for examining the stability and replicability of white matter microstructural abnormalities in ADHD across development, in order to promote the identification of early biomarkers of the disease. To that end, our results confirm that microstructure in long-range white matter pathways shows abnormality, even prior to adolescence, in a sample that is largely medication naïve and free of major comorbidity (except ODD, which did not account for results). Specifically, childhood ADHD was associated with reduced FA in bilateral temporo-occipital, and corona radiata, left cerebellar, and right fronto-parietal white matter pathways, clusters of which were broadly associated with symptoms of both inattention and hyperactivity, with many relating most significantly to symptoms of inattention. In addition, with the youngest DTI

study of ADHD to date, we also confirmed that pre-adolescent children with ADHD possess abnormal white matter microstructure in later developing bilateral frontal-limbic projection fibers. Notably, several of these white matter regions are anatomically close to those that have been identified previously as being atypical in older ADHD youth,[21, 24, 27] and thus, our findings provide converging evidence for widespread, rather than localized, atypical white matter microstructure in ADHD. As higher FA reflects greater coherence in white matter, given restriction of diffusion in dense, organized, myelinated white matter pathways,[15, 43] these findings suggest diminished white matter organization or integrity in children with ADHD.

Although white matter perturbations were widespread, the tracts involved are interesting in relation to the behavioral correlates of ADHD, as the cortical regions connected by these tracts have been implicated in ADHD and associated cognitive dysfunction (for review, see [11, 12]). Temporo-occipital and fronto-parietal white matter are similar areas to which increased FA has been correlated with aspects of attention-related cognition including response control,[44] working memory,[45] and mental arithmetic. Given this, as well as work suggesting a positive relationship between white matter integrity and brain activation,[46, 47] and the fact that long-range functional connections between brain regions strengthen across development,[48] our findings suggest that ADHD involves altered maturation in these networks. These findings converge with prior structural and functional imaging data suggesting that both cortical and subcortical structures are affected in ADHD and may help to explain prior findings of atypical brain activation,[49-51] and functional connectivity in ADHD.[52, 53] Future studies will be instrumental in clarifying these relationships.

Consistent with previous studies,[21, 54] we also found significantly reduced FA in cerebellar white matter among ADHD youth. The cerebellum's role in executive functioning is well-accepted,[55] based on its bidirectional connectivity with the cerebral cortex. Cerebellar circuits have been central in neurobiological theories of ADHD,[14] and the present findings confirm that connections between the cerebellum and associated structures are different in ADHD, not merely the cerebellum itself. [56, 57] The reproducibility of this finding across various age-ranges and the fact that the cerebellum is thought to begin myelination early in life (for review, see [58]), suggests that cerebellar white matter abnormalities may be a robust and stable feature of ADHD.

A novel result of this study was atypical FA and MD in fronto-limbic white matter, which was largely accounted for by significantly greater radial diffusion among ADHD youth. Given that radial diffusion reflects restriction perpendicular to myelin bundles and decreases with myelination,[13] these findings suggest aberrant or delayed myelin development in ADHD. This finding is striking in light of the increasing appreciation for the role of emotional dysregulation in ADHD, [59, 60] and the fact that frontolimbic white matter is among the latest to mature. [18, 19] Thus, it may be that these pathways show an altered developmental trajectory in ADHD that is no longer detectable in older children or adults with the disorder. These findings highlight the importance of examining the ADHD brain prior to adolescence, as continued experience and maturation may confound the early developmental picture.

In addition to increased MD in frontolimbic white matter, we identified two clusters of reduced MD in ADHD. In both clusters (the superior longitudinal fasciculus and posterior limb of internal capsule), axial and radial diffusivity was lower in ADHD than controls. Silk and colleagues[29] also showed reduced radial diffusion in white matter of youth with ADHD, but in association with increased (not reduced) axial diffusion. Additionally, a DTI study of youth with phenylketonuria (PKU), a childhood disease associated with ADHD-type symptoms and executive dysfunction, also reported reduced MD in patients relative to

controls.[61] While atypical myelination may contribute to the current findings, another potential explanation is that differences in the distribution of axonal fiber orientations exist, such that diffusivity is more restricted when averaged over all orientations within ADHD white matter than is the case for controls. Future analyses that account for heterogeneity in microscopic structure in individual voxels may be of utility.[62]

Although a strength of the current study is that nearly all children with ADHD were medication naïve, effects of stimulant medication on brain development remain unclear.[3, 63] Second, although this study is slightly larger than nearly all prior DTI studies of children with ADHD, power remains low. Relatedly, for the current study, we pooled ADHD subtypes and did not compare them. This was justified on grounds that it is unclear whether DSM-IV subtypes are stable or biologically defensible in children.[41] Nonetheless, subtypes may contain important biological information, a point we intend to investigate with larger samples. Likewise, although all results presented here are independent of gender, it remains necessary to determine if different developmental white matter trajectories are present in boys and girls with ADHD.

We conclude that, even by 7-9 years of age, ADHD is associated with widespread alterations in white matter microstructure in a complementary, developmentally important manner. Abnormal microstructure in early-maturing cerebellar and cortical-cortical pathways has now been replicated in children, adolescents, and adults and thus appears as a stable marker of ADHD. Conversely, alterations in late-maturing frontolimbic pathways, seen in the current study but not in older samples, may indicate an early, dynamic marker that can provide additional clues to the pathophysiology of ADHD. The current findings suggest the possibility that ADHD entails an altered developmental trajectory in the structural connectivity of the brain with neuroantomical biomarkers specific to developmental stage.

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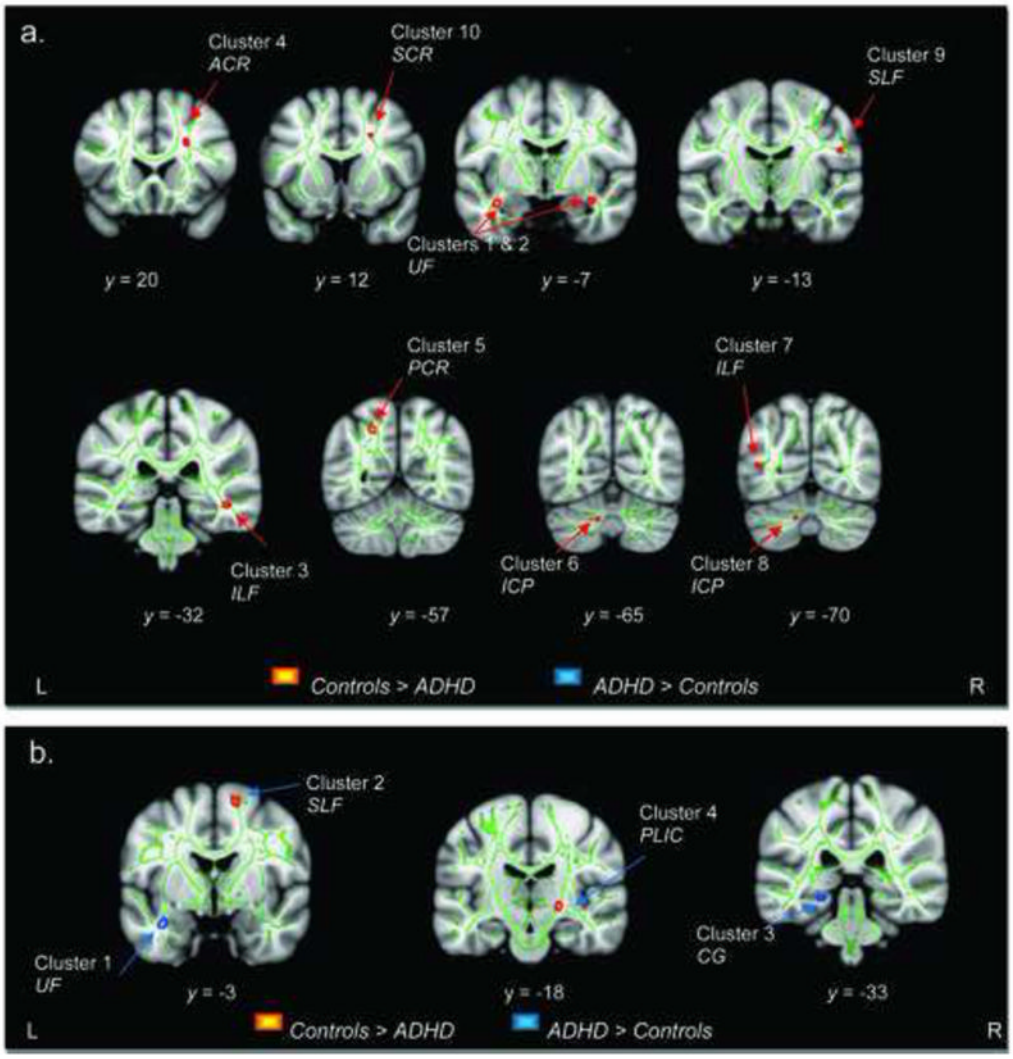

Figure 1.

Regions attention-deficit/hyperactivity disorder (ADHD) youth have significantly lower a.) fractional anisotropy (FA) (shown in red) and b.) mean diffusivity (MD) (shown in blue) compared to healthy controls (cluster volume ≥ 25 μL, voxelwise and clusterwise $\alpha < .01$; corrected *p*/voxel = 0.00000369). ACR = anterior corona radiata; CG = cingulum; ICP = inferior cerebellar peduncle; ILF = inferior longitudinal fasciculus; PLIC = posterior limb of the internal capsule; PCR = posterior corona radiata; SCR = superior corona radiata; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus.

Table 1

Demographic and clinical characteristics of each group.

	Control Group (*n* = 16)	ADHD Group (*n* = 20)	Test statistic
Demographic			
Age (years)	8.31 (0.70)	8.05 (0.69)	$t = 1.13$
Gender (% Male)	25%	65%	$\chi^2 = 5.71^{*}$
Full scale IQ	115.4 (12.9)	106.5 (12.8)	$t = 2.07^{*}$
Ethnicity (% White)	75%	70%	$\chi^2 = 0.11$
Annual home income ($k)	78.5 (35)	73.8 (55)	$t = 0.27$
Clinical			
KSADS-E Inattentive Lifetime	0.4 (0.7)	6.5 (1.9)	$t = -11.96^{***}$
KSADS-E Hyperactive Lifetime	0.4 (0.9)	4.7 (2.7)	$t = -6.03^{***}$
KSADS-E Inattentive Current	0.4 (0.7)	6.5 (1.8)	$t = -12.53^{***}$
KSADS-E Hyperactive Current	0.4 (0.9)	4.7 (2.5)	$t = -6.42^{***}$
Parent-Conners Cognitive	48.9 (7)	70.3 (8)	$t = -8.16^{***}$
Parent-Conners Hyperactive	44.6 (4)	69.8 (14)	$t = -6.71^{***}$
Teacher-Conners Cognitive	43.4 (5)	66.5 (10)	$t = -8.06^{***}$
Teacher-Conners Hyperactive	46.9 (7)	69.9 (16)	$t = -5.19^{***}$
Parent ADHD RS Inattentive Sx	4.7 (5.8)	16.2 (5.2)	$t = -6.25^{***}$
Parent ADHD RS Hyperactive Sx	3.6 (4.5)	12.5 (6.0)	$t = -4.93^{***}$
Teacher ADHD RS Inattentive Sx	1.1 (1.5)	16.7 (6.0)	$t = -10.09^{***}$
Teacher ADHD RS Hyperactive Sx	0.9 (1.3)	13.1 (8.2)	$t = -5.89^{***}$
GAD (%)	0%	10%	$\chi^2 = 0.32$
ODD (%)	6%	35%	$\chi^2 = 4.25^{*}$

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; GAD = Generalized Anxiety Disorder; K-SADS-E = Kiddie Schedule for Affective Disorders and Schizophrenia; ODD = Oppositional-Defiant Disorder; RS = Rating Scale; Sx = Symptoms.

$^{*}p < 0.05$,

$^{***}p < 0.001$.

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Table 2

Significant fractional anisotropy (FA) and mean diffusivity (MD) clusters between children with attention-deficit/hyperactivity disorder (ADHD) and controls, as well as group differences in axial and radial diffusion for each cluster.

Cluster	White Matter Tracts	# of Voxels	MNI Coordinates			Mean FA/MD				Mean Axial Diffusion (μm²/ms) (λ_1)			Mean Radial Diffusion (μm²/ms) ((λ_2+λ_3)/2)		
			x	*y*	*z*	Control	ADHD	*d*	%	Control	ADHD	*d*	Control	ADHD	*d*
Fractional Anisotropy (FA)															
1	L. UF	94	-35	-6	-20	0.48 ± 0.06	0.44 ± 0.05	0.7	8.2	1.19 ± 0.05	1.20 ± 0.04	-0.3	**0.53 ± 0.07**	**0.58 ± 0.04**	**-0.9**§
2	R. UF	63	36	-7	-17	0.44 ± 0.06	0.41 ± 0.04	0.7	7.6	1.31 ± 0.05	1.28 ± 0.05	0.6*	0.64 ± 0.07	0.66 ± 0.05	-0.4
3	R. ILF	51	44	-32	-8	0.52 ± 0.04	0.47 ± 0.05	1.1	9.5	**1.26 ± 0.08**	**1.18 ± 0.06**	**1.1**§	0.53 ± 0.05	0.57 ± 0.04	-0.7*
4	R. ACR	47	25	20	27	0.39 ± 0.04	0.35 ± 0.04	1.0	11.1	**1.10 ± 0.07**	**1.04 ± 0.05**	**1.1**§*	0.60 ± 0.04	0.62 ± 0.04	-0.6
5	L. PCR	40	-23	-57	45	0.54 ± 0.05	0.47 ± 0.09	0.9	12.9	**1.24 ± 0.09**	**1.16 ± 0.12**	**0.8**§	0.49 ± 0.05	0.53 ± 0.05	-0.8*
6	L. ICP	38	-17	-65	-33	0.36 ± 0.04	0.33 ± 0.03	0.9	10.1	0.94 ± 0.05	0.92 ± 0.05	0.5	0.54 ± 0.04	0.57 ± 0.02	-0.8**
7	L. ILF	36	-43	-70	9	0.38 ± 0.05	0.28 ± 0.07	1.6	25.3	1.05 ± 0.07	1.00 ± 0.06	0.7**	**0.57 ± 0.05**	**0.64 ± 0.05**	**-1.4**§
8	L. ICP	30	-11	-68	-32	0.40 ± 0.03	0.35 ± 0.05	1.3	13.4	0.96 ± 0.05	0.91 ± 0.05	0.9*	0.51 ± 0.03	0.54 ± 0.03	-0.9*
9	R. SLF	29	53	-13	24	0.40 ± 0.05	0.34 ± 0.05	1.1	13.4	**1.14 ± 0.06**	**1.05 ± 0.09**	**1.2**§	0.62 ± 0.04	0.64 ± 0.04	-0.6
10	R. SCR	26	21	14	34	0.40 ± 0.06	0.35 ± 0.03	0.9	10.6	**1.13 ± 0.08**	**1.07 ± 0.06**	**0.9**§	0.60 ± 0.04	0.63 ± 0.04	-0.8*
Mean Diffusivity (MD) (μm²/ms)															
1	L. UF	71	-36	-3	-24	0.75 ± 0.04	0.79 ± 0.05	-0.9	-5.3	1.18 ± 0.05	1.20 ± 0.04	-0.5	**0.54 ± 0.07**	**0.59 ± 0.04**	**-0.9**§
2	R. SLF	35	15	-3	63	0.86 ± 0.07	0.81 ± 0.05	1.0	6.6	1.23 ± 0.11	1.16 ± 0.08	0.7*	0.68 ± 0.08	0.63 ± 0.04	0.7
3	L. CG	32	-22	-33	-10	0.70 ± 0.09	0.74 ± 0.05	-0.4	-4.3	1.09 ± 0.12	1.10 ± 0.08	-0.1	**0.51 ± 0.10**	**0.55 ± 0.05**	**-0.5**§
4	R. PLIC	32	21	-18	-2	0.78 ± 0.03	0.74 ± 0.03	1.5	5.1	**1.51 ± 0.05**	**1.46 ± 0.05**	**1.1**§	**0.41 ± 0.03**	**0.38 ± 0.03**	**1.0****

Note: Bold text reflects those that were significant surviving correction for multiple comparisons. P values show statistical significance for group differences in axial and radial diffusion from the ANCOVA, controlling for gender. ACR = anterior corona radiata; CG = cingulum; *D* = Effect size using Cohen's d; ICP = inferior cerebellar peduncle; ILF = inferior longitudinal fasciculus; L = left; PLIC = posterior limb of the internal capsule; PCR = posterior corona radiata; R = right; SCR = superior corona radiata; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; % = percent difference between groups.

* $p > .05$;

** $p < .01$;

§ $p < .005$;