White Matter Alterations at 33-Year Follow-Up in Adults with Childhood Attention-Deficit/Hyperactivity Disorder

Samuele Cortese, Davide Imperati, Juan Zhou, Erika Proal, Rachel G. Klein, Salvatore Mannuzza, Maria A. Ramos-Olazagasti, Michael P. Milham, Clare Kelly, and F. Xavier Castellanos

Background: Attention-deficit/hyperactivity disorder (ADHD) is increasingly conceived as reflecting altered functional and structural brain connectivity. The latter can be addressed with diffusion tensor imaging (DTI). We examined fractional anisotropy (FA), a DTI index related to white matter structural properties, in adult male subjects diagnosed with ADHD in childhood (probands) and matched control subjects without childhood ADHD. Additionally, we contrasted FA among probands with and without current ADHD in adulthood and control subjects.

Methods: Participants were from an original cohort of 207 boys and 178 male control subjects. At 33-year follow-up, analyzable DTI scans were obtained in 51 probands (41.3 ± 2.8 yrs) and 66 control subjects (41.2 ± 3.1 yrs). Voxel-based FA was computed with tract-based spatial statistics, controlling for multiple comparisons.

Results: Probands with childhood ADHD exhibited significantly lower FA than control subjects without childhood ADHD in the right superior and posterior corona radiata, right superior longitudinal fasciculus, and in a left cluster including the posterior thalamic radiation, the retrolenticular part of the internal capsule, and the sagittal stratum ($p < .05$, corrected). Fractional anisotropy was significantly decreased relative to control subjects in several tracts in both probands with current and remitted ADHD, who did not differ significantly from each other. Fractional anisotropy was not significantly increased in probands in any region.

Conclusions: Decreased FA in adults with childhood ADHD regardless of current ADHD might be an enduring trait of ADHD. White matter tracts with decreased FA connect regions involved in high-level as well as sensorimotor functions, suggesting that both types of processes are involved in the pathophysiology of ADHD.

Key Words: ADHD, DTI, fractional anisotropy, longitudinal follow-up, neuroimaging, pathophysiology

Attention-deficit/hyperactivity disorder (ADHD)—defined by a persistent and age-inappropriate pattern of inattention, hyperactivity-impulsivity, or both (1)—is a common childhood-onset psychiatric condition, with estimated worldwide-pooled prevalence exceeding 5% in school-age children (2). Longitudinal studies have documented that impairing symptoms .of ADHD persist into adulthood in a substantial proportion (3) Such symptomatic continuity suggests continuity of pathophysiology, which has been addressed mostly through neuroimaging (4–7). Recently, the pathophysiological conceptualization of ADHD has shifted from models focused primarily on fronto-striatal regions (8) to dysfunction in widely distributed large-scale brain networks (5,9,10). Accordingly, the field has increasingly focused on abnormalities in connectivity (i.e., on white matter (WM) properties) (9,11,12).

In the present report, we focus on the assessment of WM with fractional anisotropy (FA), an index obtained with diffusion tensor imaging (DTI), which reflects a complex mixture of tissue properties, including axonal ordering, axonal density, and myelination (13). Although it is inappropriate to interpret FA as a direct measure of WM integrity, it does reflect physical differences in WM structure (13) and thus serves as a starting point for exploring structural connectivity.

A meta-analysis of DTI studies in ADHD (14), mostly conducted in children, documented abnormal FA of numerous WM tracts, including the anterior corona radiata, internal capsule, forceps minor, and cerebellar tracts. The smaller DTI literature on adults with ADHD is limited to specific brain regions of interest (15–17) or does not correct for multiple comparisons (18). Additionally, DTI studies in adults with ADHD have relied on retrospective recall of childhood symptoms, which can be questionable (19).

We report whole-brain FA analyses corrected for multiple comparisons in the largest sample to date of adults with a childhood diagnosis consistent with DSM-IV combined type ADHD (probands) and prospectively enrolled participants free of ADHD in childhood (control subjects) (20). In our previous study of gray matter structure based on the same cohorts (21), we conducted analyses based both on original (i.e., childhood) group assignment and on current diagnostic status in adulthood.

From the Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience (SC, DI, JZ, EP, MAR-O, CK, FXC); Anita Saltz Institute for Anxiety and Mood Disorders (RGK, SM), Child Study Center, New York University Langone School of Medicine; Center for the Developing Brain (MPM), Child Mind Institute, New York; Nathan Kline Institute for Psychiatric Research (SM, MPM, FXC), Orangeburg, New York; Child Neuropsychiatry Unit (SC), G. B. Rossi Hospital, Department of Life Science and Reproduction, Verona University, Verona, Italy; UMR_S INSERM U 930 (SC), CNRS ERL 3106, François-Rabelais University, Child Psychiatry Centre, University Hospital, Tours, France; Duke-NUS Graduate Medical School (JZ), Neuroscience and Behavioral Disorders Program, and the Agency for Science, Technology and Research, Neuroscience Research Partnership, Singapore; and the Neuroingenia Clinical and Research Center (EP), México, D.F., México.

Address correspondence to Samuele Cortese, M.D., Ph.D., Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, Child and Adolescent Psychiatry, New York University Child Study Center, One Park Avenue, 7th Floor, New York, New York 10016; E-mail: samuele.cortese@gmail.com.

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Similarly, here our first objective was to contrast FA in adulthood between probands with childhood ADHD and control subjects without childhood ADHD. Our prior analyses (21) revealed reduced cortical thickness in probands relative to control subjects in parietal, temporal, frontal, and occipital regions. Analyses of gray matter density with voxel based morphometry (VBM) generally echoed these findings and also revealed decreased gray matter density in caudate, thalamus, and cerebellum. Accordingly, we expected to find alterations of FA in probands with childhood ADHD relative to control subjects without childhood ADHD in tracts connecting the gray matter regions that were abnormal in our previous analyses (21).

As in our prior study (21), the second objective was to contrast probands with persistent ADHD and those in remission with control subjects free of current ADHD symptoms in adulthood and with each other. Analyses based on current diagnosis in adulthood allow comparability with cross-sectional studies of adults with ADHD. They also allowed us to examine FA correlates of persistence versus remission in ADHD for the first time.

Methods and Materials

Participants

The study was approved by the institutional review boards of New York University Langone Medical Center and New York University. Participants provided written informed consent and were compensated for participating.

Probands originally consisted of 207 6- to 12-year-old middle class Caucasian boys referred to a research clinic from 1970 to 1978 (mean ± SD: 8.3 ± 1.6 years) (22–24). Inclusion criteria were: school referral because of behavior problems, elevated parent and teacher hyperactivity ratings, behavior problems in multiple settings, IQ ≥ 85, and English speaking parents. Children with a pattern of aggressive or antisocial behavior were excluded to rule out comorbid conduct disorder. Psychosis and neurological disorders were also exclusionary. As detailed elsewhere (25), all probands would have met criteria for DSM-IV ADHD combined type. Of 207 ADHD probands, 182 were treated with methylphenidate for an average of 2.2 ± 1.6 years. Three follow-up (FU) waves were conducted, when probands were 18.4 ± 1.3, 25.0 ± 1.3, and 41.2 ± 2.7 years (FU18, FU25, and FU41, respectively). Comparison male subjects (n = 178) matched for age, social class, and geographic residence, were recruited at FU18 from the same medical center among children seen for routine physical exams whose record history and interview with parents did not indicate behavior problems during elementary school. At FU41, 135 of 207 male probands (65%) and 136 of 178 male control subjects (76%) participated in the FU. The Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition (SCID-I/NP) (26) was administered by clinicians, inquiring about function during the interval between FU25 and FU41. A special interview, Assessment of Adult Attention Deficit Hyperactivity Disorder (21,27), was developed for diagnosing DSM-IV ADHD in adults. Current ADHD was defined as meeting DSM-IV criteria during the preceding 6 months. Participants diagnosed as having ADHD-not otherwise specified (NOS) at FU41 had fewer than the required number of DSM-IV criteria but reported significant impairment or distress associated with these symptoms.

DTI Acquisition

Anatomic T1-weighted scans were obtained on a 3T Siemens Trio (Siemens, Munich, Germany) with an 8-channel head coil (probands: n = 18, control subjects: n = 14, total: n = 32) or a 3T Siemens Allegra with a single-channel head coil (probands: n = 33, control subjects: n = 52, total: n = 85) with the following parameters: repetition time = 2100 msec; flip angle = 12°; slice thickness = 1.5 mm; inversion time = 1100 msec; matrix: = 192 × 256; field of view = 172.5 mm. Echo time was 3.87 msec on the Trio and 3.90 msec on the Allegra.

The DTI was acquired in one nonweighted and six diffusion-weighted noncollinear directions with an echo-planar sequence with diffusion weighting (b value) of 1000 smm^{-1}. A dual spin echo was used to minimize distortion due to eddy currents. Imaging parameters were: repetition time = 6100 msec; flip angle = 90°; field of view = 178 × 219; matrix = 104 × 128; voxel size = 1.71 × 1.71 × 4 mm; number of averages = 4. Echo time was 102 msec on the Allegra and 92 msec on the Trio.

Image Preprocessing

Motion correction was performed by applying 9 degrees of freedom linear registration to a standard Montreal Neurological Institute template. Eddy-current and echo planar image distortion-related corrections were also performed. Diffusion gradients were rotated to improve consistency with the motion parameters. Diffusion images were visually inspected for motion effects by two investigators (S.C., J.Z.). Data were discarded if the interslice displacement was more than 3 mm. Data for each of the six corrected directions were used to fit the tensor parameters. Diffusion tensors were fitted for each voxel to obtain FA images, which were registered to FMRIB58_FA standard space image with 1-mm^3 resolution with the nonlinear registration tool FNIRT (28). We then applied tract-based spatial statistics (TBSS) (29) to carry out a voxel-wise analysis of FA data within major WM pathways throughout the brain. The TBSS minimizes problems of intersubject registration by first determining a mean FA "skeleton," representing only the center of major WM fiber tracts, then mapping the DTI data of each participant directly onto the skeleton. Analysis of FA differences is thus restricted to regions that represent, with high confidence, only the center of equivalent WM tracts of each individual. A standard FA template was used, and the standard space FA data of each participant were projected onto the FA template with the standard preprocessing scripts provided with the FMRIB Software Library (FSL) TBSS and adapted for group features (29). The resultant skeletonized FA images were used for statistical analyses.

Statistical Analyses

Group differences in sample characteristics were tested with independent-samples t tests or χ^2 tests. The DTI data were analyzed with FSL 4.1.5 (30). We examined voxelwise cross-subject spatial statistics of FA values with permutation-based nonparametric testing (FSL RANDOMISE) on the skeletonized FA images. First, we compared probands with childhood ADHD to control subjects without childhood ADHD. Then, to test whether FA differed as a function of current ADHD, we classified probands as to whether they had ADHD at FU41 or not, thus generating two proband subgroups, "probands with persistent ADHD" and "probands with remitted ADHD." They were contrasted with control subjects who did not meet criteria for ADHD-NOS at FU41 ("non-ADHD control subjects") (20). Contrasts were: 1) probands with persistent ADHD versus non-ADHD control subjects; 2) probands with remitted ADHD versus non-ADHD control subjects; and 3) probands with persistent ADHD versus probands with remitted ADHD. In each contrast, age and scanner model were covaried (supplementary analyses were performed limited

to the 85 datasets obtained on the Allegra scanner, to address concerns with regard to possible dependence of DTI parameters on scanner type and sequence). We corrected for multiple comparisons with threshold-free cluster enhancement (31). The Johns Hopkins University DTI-based WM atlas, available in FSL (30), was used to label the WM tracts.

Results

Subjects

A total of 152 participants were scanned at FU41, of whom 144 (61 probands, and 83 control subjects) underwent diffusion-weighted scans. The DTI data for 10 probands and 17 control subjects failed quality criteria, leaving 51 probands and 66 control subjects with analyzable DTI data. Rates of magnetic resonance imaging (MRI) refusal and failure to schedule or locate subjects did not differ significantly between probands and control subjects (45% vs. 43%). However, a smaller proportion of probands (32%) than control subjects (48%) were scanned. This discrepancy reflects a significantly higher rate of unavoidable factors in probands (i.e., deaths, incarcerations, or MRI exclusions) than in control subjects (27% vs. 12%, respectively; $p < .001$) (20). Within both proband and control groups, individuals scanned and those not scanned did not differ significantly on age at referral, childhood IQ, socioeconomic status, Teachers Conners Hyperactivity Factor scores (32), and rates of mental disorders at FU18 (ADHD, antisocial personality disorder, mood or anxiety disorders) (21). However, scanned probands had significantly higher rates of substance use disorders (SUD) at FU18 than not-scanned probands (25% vs. 8%; $p = .02$) (21). Scanned individuals with or without analyzable DTI data did not differ significantly in scanner type ($p = .99$), age ($p = .53$), or full scale IQ ($p = .91$) at FU41.

Fifteen of the 51 probands with analyzable DTI met DSM-IV criteria for current ADHD: 6 (11.8%) with inattentive type; 6 (11.8%) with hyperactive-impulsive type; and 3 (5.9%) with combined type. Twenty-five probands (49%) were classified as remitters (Table 1). Probands ($n = 11$, 21.6%) and control subjects ($n = 19$, 28.7%) with ADHD-NOS at FU41were excluded from subgroup analyses, as in our prior study (21). Therefore, we used data from 47 (66 − 19) non-ADHD control subjects for subgroup analyses (21). Forty-seven probands (92%) had been treated with methylphenidate in childhood. Co-occurring ongoing SUD did not differ between probands with childhood ADHD and control subjects without childhood ADHD (22% vs. 21%, respectively) or among probands with persistent ADHD, those in remission, or non-ADHD control subjects (Table 1).

DTI Analyses

Table 2 and Figure 1 present FA differences between probands and control subjects. Probands with childhood ADHD ($n = 51$) exhibited significantly lower FA than control subjects without childhood ADHD ($n = 66$), adjusting for age and scanner model, in two large sets of clusters, one in each hemisphere. The left hemisphere cluster encompassed the sagittal stratum and the retrolenticular part of the internal capsule, including the posterior thalamic radiation. The right hemisphere cluster comprised the superior longitudinal fasciculus (SLF) II and the posterior and superior corona radiata.

Probands with persistent ADHD ($n = 15$) exhibited significantly lower FA than non-ADHD control subjects ($n = 47$) in a right hemisphere tract encompassing the sagittal stratum, external capsule, retrolenticular part of the internal capsule, and the anterior corona radiata (Figure 2, and Table 2). Probands with remitted ADHD ($n = 25$) also exhibited significantly lower FA than non-ADHD control subjects in right superior and posterior corona radiata (Figure 3, and Table 2). Probands with persistent ADHD and those who had remitted ADHD did not differ significantly in FA when correcting for multiple comparisons or even at $p < .01$, uncorrected. In no instance did probands exhibit significantly higher FA than control subjects. Analyses limited to the 85 scans obtained with the Allegra scanner revealed similar results, albeit at a somewhat reduced level of statistical significance ($p < .15$, corrected; Table S1 in Supplement 1).

Discussion

This is the first DTI study in adults with ADHD established in childhood. As expected, we found significantly decreased FA in probands relative to control subjects, regardless of ADHD diagnosis at mean age 41 years, in WM tracts connecting gray matter regions that we found to be abnormal in the same cohorts (21). Fractional anisotropy in probands with childhood ADHD was decreased relative to control subjects without childhood ADHD in a left hemisphere cluster encompassing the sagittal stratum and the retrolenticular part of the internal capsule and in a right

Table 1. Demographic and Clinical Characteristics of Participants with Analyzable DTI Data at FU41

	Prob ($n = 51$)	CS ($n = 66$)	p(2-sided)	ADHD+ ($n = 15$)	ADHD− ($n = 25$)	Non-ADHD CS[a] ($n = 47$)	p(2-sided)	Post Hoc LSD
Age at FU41	41.3 (2.8)	41.2 (3.1)	.81	41.8 (3.0)	41.3 (2.6)	41.1 (3.0)	.74	
SES at FU41	3.4 (1.1)	2.4 (1.0)	<.001	3.7 (1.2)	3.2 (1.1)	2.4 (1.1)	<.001	CS> ADHD−: $p = .01$ CS > ADHD+: $p < .001$
Comorbid SUDs[b]	11 (21.6)	14 (21.2)	.59	4 (26.7)	5 (20.0)	8 (17.0)	.71	
Full Scale IQ at FU41[c]	101.3 (13.7)	108.9 (16.0)	.01	99.3 (13.0)	103.8 (13.1)	111.1 (14.3)	.01	CS> ADHD−: $p = .08$ CS > ADHD+: $p = .04$
Type of Scan			.09				.25	
Siemens Allegra	33 (64.7)	52 (78.8)		9 (60.0)	18 (72.0)	38 (80.9)		
Siemens Trio	18 (35.3)	14 (21.2)		6 (40.0)	7 (28.0)	9 (19.1)		

Values are mean (SD) or *n* (%), unless otherwise indicated. "ADHD+" and "ADHD−" refer to attention-deficit/hyperactivity disorder (ADHD) probands with persistent and remitted ADHD, respectively.

CS, control subjects; DTI, diffusion tensor imaging; FU41, follow-up at mean age 41 years; LSD, least significant difference; Prob, probands; SES, socioeconomic status; SUDs, substance use disorders.

[a]Excluding those ($n = 19$) with ADHD-not otherwise specified at FU41.

[b]Definite diagnoses, current.

[c]Data available for 46 probands and 61 control subjects.

Table 2. Significant FA Clusters Between Probands and CS

Cluster	WM Tract	*n* Voxels	MNI Coordinates (Peak Voxel) x	y	z	t_{max}	*p*
Probands with Childhood ADHD < CS without Childhood ADHD							
1	Posterior thalamic radiation L (including optic radiation)	205	−40	−42	−3	3.7	.02
2a	Retrolenticular part of internal capsule L	94	−40	−35	−2	4.1	.02
2b	Sagittal stratum L (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	129	−41	−38	−6	3.4	.02
3	Superior longitudinal fasciculus II R	95	30	−40	34	3.3	.02
4	Posterior corona radiata R	147	23	−42	36	3.0	.02
5	Superior corona radiata R	94	21	−15	41	2.8	.03
Probands with Persistent ADHD < Non-ADHD CS							
1	Sagittal stratum R (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	266	36	−21	−6	2.8	.03
2	External capsule R	263	34	3	−10	2.9	.03
3	Retrolenticular part of internal capsule R	38	40	−32	−3	2.7	.04
4	Anterior corona radiata R	13	23	28	−4	3.2	.05
Probands with Remitted ADHD < Non-ADHD CS							
1	Posterior corona radiata R	123	20	−44	38	4.3	.02
2	Superior corona radiata R	72	22	−28	39	3.3	.03

$p < .05$, corrected, controlling for age and scanner type.

ADHD, attention-deficit/hyperactivity disorder; CS, control subjects; FA, fractional anisotropy, L, left; MNI, Montreal Neurological Institute; R, right; WM, white matter.

hemisphere cluster comprising the superior longitudinal fasciculus II, posterior corona radiata, and superior corona radiata. In subgroups defined by current ADHD diagnoses (i.e., in adulthood), probands with persistent ADHD exhibited significantly reduced FA relative to non-ADHD control subjects in several tracts, two of which overlapped with those found in the all-inclusive analysis, albeit in the opposite (right) hemisphere. Probands with ADHD in remission also had significantly lower FA than non-ADHD control subjects in right hemisphere tracts. Probands with persistent and remitted ADHD did not differ significantly from each other in any tract.

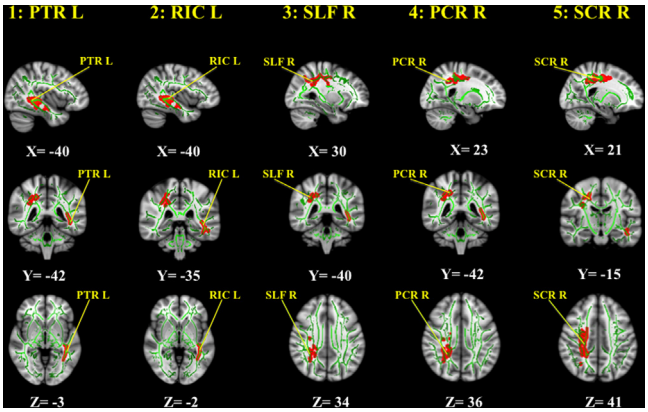

Figure 1. Regions where probands with childhood attention-deficit/hyperactivity disorder ($n = 51$) had significantly lower fractional anisotropy than control subjects without childhood attention-deficit/hyperactivity disorder ($n = 66$) (threshold-free cluster enhancement, $p < .05$, corrected). The mean fractional anisotropy skeleton is represented in green. Significantly different clusters have been thickened with the FMRIB Software Library option "tbss_fill" (30) (in a yellow-red scale) for visualization. The clusters are labeled according to the John Hopkins University diffusion tensor imaging-based white-matter atlas (ICBM-DTI-81), available in FMRIB Software Library (30). Although slices show all significant clusters, arrows indicate the specific cluster of interest for each column. PCR R, posterior corona radiata right; PTR L, posterior thalamic radiation left; RIC L, retrolenticular part of internal capsule left; SCR R, superior corona radiata right; SLF R, superior longitudinal fasciculus right.

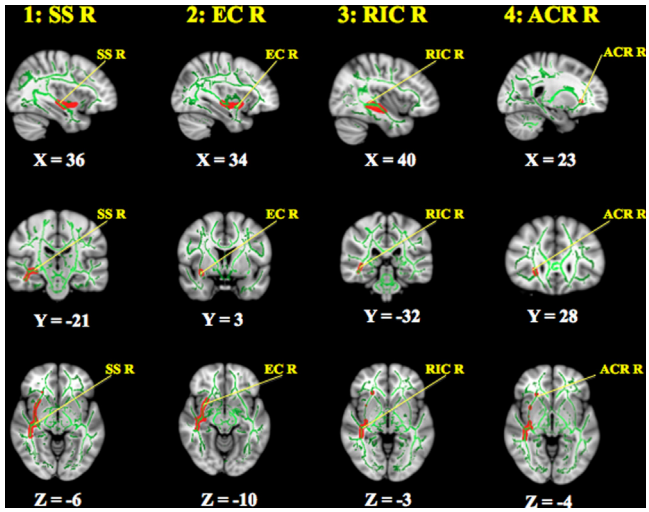

Figure 2. Regions where probands with persistent attention-deficit/hyperactivity disorder ($n = 15$) had significantly lower fractional anisotropy than non–attention-deficit/hyperactivity disorder control subjects ($n = 47$) (threshold-free cluster enhancement, $p < .05$, corrected). The mean fractional anisotropy skeleton is represented in green. Significantly different clusters have been thickened with the FMRIB Software Library option "tbss_fill" (30) (in a yellow-red scale) for visualization. The clusters are labeled according to the John Hopkins University diffusion tensor imaging-based white-matter atlas (ICBM-DTI-81), available in FMRIB Software Library (30). ACR R, anterior corona radiata right; ECR R, external capsule right; RIC R, retrolenticular part of internal capsule right; SS R, sagittal stratum right.

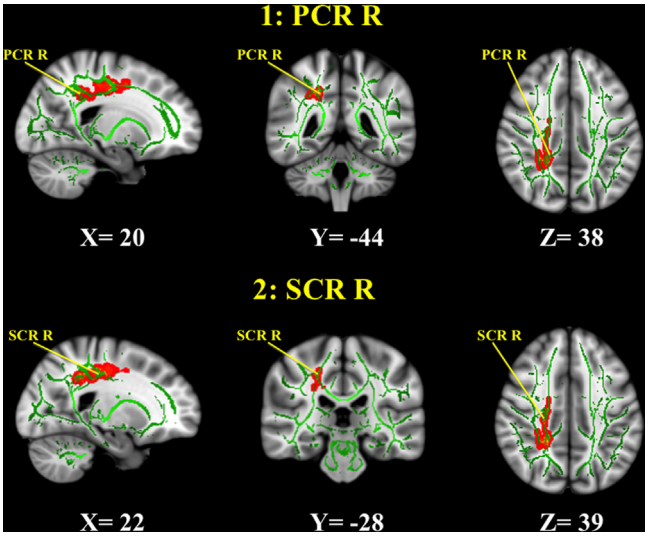

Figure 3. Regions where probands with remitted attention-deficit/hyperactivity disorder ($n = 15$) had significantly lower fractional anisotropy than non–attention-deficit/hyperactivity disorder control subjects ($n = 47$) (threshold-free cluster enhancement, $p < .05$, corrected). The mean fractional anisotropy skeleton is represented in green. Significantly different clusters have been thickened with the FMRIB Software Library option "tbss_fill" (30) (in a yellow-red scale) for visualization. The clusters are labeled according to the John Hopkins University diffusion tensor imaging-based white-matter atlas (ICBM-DTI-81), available in FMRIB Software Library (30). PCR R, posterior corona radiata right; SCR R, superior corona radiata right.

Probands with Childhood ADHD Relative to Control Subjects without Childhood ADHD

We found reduced FA in probands in tracts connecting regions involved in higher-level cognitive as well as in sensorimotor functions including, in particular, visual processing. These are: left sagittal stratum; left retrolenticular part of internal capsule (including posterior thalamic radiation); and right superior longitudinal fasciculus II.

Left Sagittal Stratum. This tract contains fibers of the inferior fronto-occipital fasciculus (IFO), which connects the lateral aspects of the frontal and occipital lobes as well as prefrontal cortex to auditory (Brodmann area [BA] 22) and visual association cortex (BA 20–21). The IFO is implicated in attention set-shifting abilities (33), which are deficient in ADHD (34–36). Fractional anisotropy in the IFO was reduced in a study of adults with ADHD (18). Additionally, the sagittal stratum contains fibers of the inferior longitudinal fasciculus (ILF), which was reported abnormal in children with ADHD (37). The ILF relays visual information from occipital to temporal cortex, subserving visual perception and object recognition (38). Alterations in this tract might underlie visual memory deficits in ADHD (39).

Left Retrolenticular Part of Internal Capsule (including posterior thalamic radiation). Consistent with findings in children with ADHD (40), probands had reduced FA in the retrolenticular part of internal capsule, mostly within the posterior thalamic radiation, which contains fibers of the optic radiation carrying visual information from the lateral geniculate nucleus to the occipital lobe (41). This finding further underscores the possible role of dysfunctions within the visual system in ADHD. Although largely overlooked in the ADHD literature, partly because of the focus on fronto-striatal dysfunctions (8), anomalies of the visual system have been reported in structural (42) and functional (43) MRI studies. Additionally, event-related electrophysiological and MRI studies concur in suggesting a possible deficit in early visual processing in ADHD (44,45).

Right Superior Longitudinal Fasciculus. The SLF II is a pathway connecting dorsolateral prefrontal regions and caudal-inferior parietal lobe (46) that has been found to be abnormal in adults (17) and children (37,47) with ADHD. Visual perceptual information carried by the SLF II from the parietal lobe to the prefrontal cortex allows prefrontal cortex to regulate focusing attention in space (46). The SLF II also subserves spatial working memory (48), a consistent executive function deficit in children (49,50) and adults (51) with ADHD.

Also in the right hemisphere, we found two clusters with reduced FA in probands in the superior and posterior corona radiata, consistent with results in children with ADHD (52). The superior and posterior corona radiata include descending sensorimotor fibers contributing to the corticospinal tract (53,54). Alterations in these tracts might underpin sensorimotor deficits in ADHD (55).

Fractional anisotropy in the anterior corona radiata, found reduced in children with ADHD (52,56–58), did not differ significantly in probands versus control subjects at $p < .05$, corrected. However, at a lower threshold of $p = .12$, corrected, a significant FA reduction in the anterior corona radiata in probands versus control subjects emerged (data not shown). Discrepancies between our findings and previous results might be ascribable to different analytical procedure (i.e., TBSS was not implemented in early studies). We note that a prior study using TBSS in children with ADHD found increased rather than reduced FA in several tracts, which was speculatively linked to decreased neuronal branching in ADHD (37).

Relationship of WM Findings to Cortical Thickness and VBM Findings in this Study Cohort

The WM tracts that differentiated probands from control subjects connect brain regions that we found to be abnormal in cortical thickness and VBM (21). Specifically, probands had relatively: reduced cortical thickness in right dorsolateral (right middle frontal gyrus, BA 9) and right inferior parietal regions, which are connected by the right SLF II; reduced cortical thickness in the right (as well as left) precentral gyrus (BA 6), from which descending fibers of the superior and posterior corona radiata depart; reduced cortical thickness in the left frontal pole and reduced gray matter density in the left middle temporal gyrus (BA 21), connected by the IFO; reduced cortical thickness and gray matter density in left temporal and occipital regions, connected by the ILF; and reduced gray matter density in the left temporo-occipital cortex (BA 37; involved in visual recognition) as well as right occipital areas 18 and 19, which are targets of the posterior thalamic radiation. We did not find significant alterations in tracts connected with cerebellar regions, in contrast with our finding of reduced VBM in cerebellum (21) and reports of abnormal FA in cerebellar peduncles in children with ADHD (57,59,60). The only other voxel-wise DTI study in ADHD adults (18) also failed to find significant alterations in cerebellar-related tracts.

Study Findings in Relation to Neural Models of ADHD

Summarizing, we found evidence of WM alterations in tracts connecting regions involved in higher-level cognitive functions as well as sensory and motor functions. In response to an early model of ADHD highlighting executive functions (61), imaging studies have tended to focus on prefrontal and related regions

and ignore those involved in more basic sensory and motor processes. In particular, abnormalities in visual areas have been overlooked, even when abnormal results were reported [e.g., (62,63)]. A recent meta-analysis (43) of functional MRI studies of ADHD documented ADHD-related abnormalities in systems subserving higher-level cognitive functions, such as the frontoparietal, dorsal attention, and default network, as well as regions underpinning sensory (including visual) and motor functions.

Our findings of significant FA differences in ADHD probands relative to control subjects, regardless of current ADHD diagnosis, support the interpretation that WM alterations might represent an enduring neurobiological trait independent of syndromic remission. Because this is a cross-sectional DTI assessment embedded in a prospective clinical FU, we cannot establish whether significant reductions in FA reflect recent or early and enduring alterations in ADHD. The latter seems most likely in light of prior results of FA deficits in children with ADHD (52) and the lack of differences between probands with remitted and persistent ADHD.

Probands with Persistent ADHD Relative to Non-ADHD Control Subjects

The analysis in probands with childhood ADHD versus control subjects without childhood ADHD revealed FA differences in both hemispheres. By contrast, individuals with persistent ADHD, relative to non-ADHD control subjects, showed reduced FA only in the right hemisphere. However, analyses with a relaxed statistical threshold ($p < .09$, corrected, data not shown) revealed that these tracts also tended to be abnormal in the left hemisphere. Thus, hemispheric differences likely reflect threshold effects. At $p = .05$, corrected, reduced FA in probands with persistent ADHD versus non-ADHD control subjects was found in two clusters (i.e., sagittal stratum and the retrolenticular part of the internal capsule), which had been detected in the left hemisphere in the all-inclusive analysis.

Three additional clusters of reduced FA in probands with persistent ADHD were found in the right anterior corona radiata and external capsule. Several groups have reported FA reductions in the anterior corona radiata in ADHD (52,56–58). The anterior corona radiata contains WM fibers connecting the anterior cingulate cortex (ACC) to the striatum (64). Abnormalities of the dorsal ACC in ADHD have been found in both structural (65–67) and functional data (68,69). The dorsal ACC subserves multiple functions that are altered in ADHD, such as attention, target detection, response selection/inhibition, error detection, and motivation (70). Finally, external capsule FA was reduced in a study of adolescents with very low birth weight and ADHD (71). In no instance did probands with persistent ADHD at FU41 have significantly higher FA than non-ADHD control subjects, consistent with findings from the contrast "probands with childhood ADHD versus control subjects without childhood ADHD."

Because of methodological differences, comparisons with prior studies of FA in adults with ADHD are not straightforward. Makris *et al.* (17) found significantly lower FA values in the cingulum bundle and in the SLF II in adults with ADHD versus control subjects; Dramsdahl *et al.* (15) showed ADHD-related reduction of FA in the isthmus/splenium of the corpus callosum; Konrad *et al.* (16) reported lower FA in the left ILF in adults with ADHD versus control subjects. However, all three studies used a region-of-interest approach, whereas we did not limit our investigation to specific regions. In an earlier study, Konrad *et al.* (18) reported reduced FA bilaterally in medial orbitofrontal WM and in the right anterior cingulate bundle and elevated FA bilaterally in temporal WM structures in the ADHD group. However, differently from ours, these results were uncorrected for multiple comparisons.

Probands with Remitted ADHD Relative to Non-ADHD Control Subjects and Probands with Persistent ADHD

This study provided the first opportunity to investigate FA in relation to ADHD remission. Probands with remitted ADHD exhibited significantly lower FA than non-ADHD control subjects in right superior and posterior corona radiata. These two tracts were also found when contrasting probands with childhood ADHD and control subjects without childhood ADHD. However, probands with remitted ADHD did not differ significantly from probands with current ADHD even though the former had less than a total of two ADHD symptoms on average (data not shown). This suggests that decreased FA in certain WM tracts predominantly reflects childhood ADHD status, independently of current diagnostic status, presumably reflecting the influence of genetic factors.

Study Limitations

We were able to analyze imaging data for only 25% of the original cohort of ADHD probands and 37% of comparison subjects. However, probands and control subjects studied were representative of the original sample, and the probands studied did not differ significantly from lost subjects on nearly all clinical and demographic variables, except for significantly higher rates of SUD at FU18 in scanned probands. However, probands and control subjects who were scanned had nearly identical rates of current SUD at FU41. Second, our subjects were exclusively Caucasian men, because the number of originally diagnosed women with ADHD was too small ($n = 19$) for meaningful study. Thus, our results might not generalize to women or to other racial or ethnic groups. However, this constraint avoided potential confounds from possible sex, ethnic, or socioeconomic differences. Exclusion of conduct disorder comorbidity in childhood also averted confusion as to the origin of the FA deficits we found. Third, our DTI acquisition protocol included only six directions, which was standard when the study was planned. However, imprecision in FA values resulting from the use of only six directions of diffusion sensitization would affect FA measures in control subjects and probands equally and should not have biased group differences. For logistic reasons, we used two different scanners. Fortunately, group representation did not differ significantly across the scanners, and we performed all analyses with scanner model as a covariate. We also confirmed that the same pattern of results held up when analyses were limited to the single scanner on which most studies were performed. Fourth, we cannot comment on the effects of stimulant treatment in childhood on FA, because all but four of the probands received stimulant treatment in childhood for an average of approximately 2 years. However, prior studies have failed to detect stimulant effects on FA (47,59,72). Finally, despite the substantial overall size of the sample, sub-analyses on the basis of current diagnosis were based on small groups, which limited statistical power. Thus the lack of differences between probands in remission and those with persistent ADHD should be viewed as suggestive.

Conclusions

We found evidence of decreased FA, reflecting altered WM properties, in adults with childhood ADHD, regardless of presence or absence of current ADHD, suggesting that FA alteration might be an enduring trait related to ADHD. The implicated WM tracts connect regions involved in high-level as well as

sensorimotor functions, suggesting that both types of processes might be involved in the pathophysiology of ADHD.

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