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Archival Report

White Matter Microstructure in Attention-Deficit/Hyperactivity Disorder: A Systematic Tractography Study in 654 Individuals

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate levels of inattention and/or hyperactivity-impulsivity. ADHD has been related to differences in white matter (WM) microstructure. However, much remains unclear regarding the nature of these WM differences and which clinical aspects of ADHD they reflect. We systematically investigated whether fractional anisotropy (FA) is associated with current and/or lifetime categorical diagnosis, impairment in daily life, and continuous ADHD symptom measures.

METHODS: Diffusion-weighted imaging data were obtained from 654 participants (322 unaffected, 258 affected, 74 subthreshold; 7–29 years of age). We applied automated global probabilistic tractography on 18 major WM pathways. Linear mixed-effects regression models were used to examine associations of clinical measures with overall brain and tract-specific FA.

RESULTS: There were significant interactions of tract with all ADHD variables on FA. There were no significant associations of FA with current or lifetime diagnosis, nor with impairment. Lower FA in the right cingulum angular bundle was associated with higher hyperactivity-impulsivity symptom severity ($p_{familywise\ error}$ = .045). There were no significant effects for other tracts.

CONCLUSIONS: This is the first time global probabilistic tractography has been applied to an ADHD dataset of this size. We found no evidence for altered FA in association with ADHD diagnosis. Our findings indicate that associations of FA with ADHD are not uniformly distributed across WM tracts. Continuous symptom measures of ADHD may be more sensitive to FA than diagnostic categories. The right cingulum angular bundle in particular may play a role in symptoms of hyperactivity and impulsivity.

Keywords: ADHD, Diffusion MRI, Dimensional, Neuroimaging, Tractography, White matter

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age-inappropriate levels of inattention (IA) and/or hyperactivity-impulsivity (HI). Approximately 5% of children worldwide are diagnosed with ADHD, and about 15% of youths with ADHD retain a full diagnosis, while around 70% retain impairing symptoms of the disorder in adulthood (1,2). Using diffusion-weighted imaging (DWI), studies have reported alterations in white matter (WM) microstructural properties across the lifespan of people with ADHD, some of which had an overlapping sample with the current study (summarized in Table S12) (3–11). Generally, however, limited sample sizes and methodological differences between studies contribute to inconsistencies in the locations and directions of findings thus far, including studies within the same sample (Table S12). Previous studies leave several unanswered questions that are critical for understanding the clinical relevance of DWI findings,

especially whether WM microstructural properties are associated with 1) trait versus state effects in ADHD, 2) continuous symptom measures versus categorical diagnosis of ADHD, and 3) clinical impairment in ADHD. Here, we applied automated tractography to DWI data from a large cohort of participants with and without ADHD to address such questions.

DWI measures the magnitude and direction of water diffusion, which in WM reflects the underlying organization of axons and their surrounding myelin (12–14). With diffusion tensor analysis, different metrics of water diffusion are calculated in each voxel, such as the degree of its directional preference (fractional anisotropy [FA]), which is the most commonly investigated metric and the one we focus on here. Although FA is not a direct measure of physiological cellular properties, it is assumed to reflect a combination of the degree of parallel organization of axons, their packing density, and the amount and integrity of their myelin sheath (15,16). In ADHD

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case-control studies to date, lower FA in ADHD has been found in many locations, most frequently in interhemispheric, frontal, and temporal regions; yet, elevated FA has also been reported (3). Thus, many case-control studies show some differences in FA in ADHD, but the nature and anatomical locations of these findings are inconsistent.

FA has mostly been related to diagnosis at a single time point, typically at the time of DWI acquisition. However, remission occurs in some patients, as do fluctuations in symptom severity and impairment over time (2). Typical case-control designs cannot disentangle stable lifetime trait effects associated with ADHD from those associated with ADHD as a current state. A better understanding of these dynamics has implications for assumptions behind genetic liability for ADHD, for the nature of the neural mechanisms underlying ADHD, and their potential receptiveness to treatment. Here, we refer to associations based on patients' current diagnoses as "state" effects, and to associations related to ever-affected individuals regardless of current diagnosis as "trait" effects. Trait effects remain identifiable in remittent patients, pointing to the possibility that the diagnosis of ADHD at any point leaves an indelible "mark" on WM that persists throughout life, regardless of the disorder's progression (10). In longitudinal studies, decreased FA has been found as a trait effect of ADHD in thalamocortical tracts and the superior longitudinal fasciculus, irrespective of diagnostic outcome. However, in other studies, no such trait effects were found (10,17). Larger sample sizes combined with sophisticated DWI analytical techniques may clarify inconsistencies in these previous findings.

Unlike the hard line of diagnostic category, ADHD symptoms are continuously distributed throughout the population, and the boundary between those with and without the disorder is ill-defined (18–20). Considering continuous variables of symptom severity, rather than categorical diagnosis, could increase power to detect ADHD-related cognitive processes and brain traits that are also continuously distributed. Nonclinical "control" participants may also exhibit subclinical ADHD characteristics, and within patient groups, there is considerable variation in symptom severity. Dimensional analyses allow for modeling of the entire spectrum of ADHD, from minor subthreshold symptoms to clinically extreme symptoms (21). Generally, however, DWI studies that have applied dimensional analyses have been inconsistent in terms of anatomical location and have suggested that within the patient population, increased symptom severity ratings are associated with higher FA in widespread brain regions (9,22). Given that the categorical diagnosis of ADHD has generally been associated with reduced FA, a more in-depth study of these counterintuitive effects is warranted.

The sole presence of (sufficient) symptoms does not constitute a diagnosis of ADHD. For a clinical diagnosis, symptoms must be accompanied by impairment in daily functioning at home, at school or work, and/or in social settings. The degree of impairment does not directly map onto diagnosis or symptom severity scores. To understand the nature of case-control differences and their contrast with associations with symptom dimensions, an understanding of how clinical impairment is associated with brain differences is equally necessary. Although impairment may be a more subjective measure than symptom criteria, it is arguably the most impactful factor in the quality of life of patients. Impairment may be predictive of emotional lability in ADHD, independent of symptom severity (23). Magnetic resonance imaging (MRI) studies that considered clinical impairment specifically, independent of diagnosis or symptom severity, are scarce to date.

An additional origin of discrepancies between studies may be found in methodological differences. The use of voxelwise analyses in the presence of crossing fibers and anatomical differences in tract width and shape can lead to ambiguity in the anatomical location of DWI findings. Additionally, residual effects of head motion after realignment tend to be associated with DWI outcome measures but are not always taken into account (3). Previous tractography methods required user interaction (e.g., manually draw regions of interest or set thresholds for path angle and length), involved a priori selection of tracts, and employed local tractography (24). In an effort to improve large dataset analysis in a data-driven manner, we applied tractography to one of the largest cohorts of individuals with ADHD and healthy controls. We applied global probabilistic tractography in combination with anatomical knowledge of the tract's location and shape, allowing fully automated tractography of several major WM tracts. In summary, in the largest DWI analysis of ADHD to date, we investigated the relationship of WM microstructure with lifetime and current ADHD diagnosis, dimensional scales of current symptoms, and ADHD-related impairment.

METHODS AND MATERIALS

Participants

A full description of the study design is available in previous work (25). Subjects were part of the IMAGE (International Multicenter ADHD Genetics) study (wave 1 [W1]), which began in 2003 and included participants originally recruited with an ADHD diagnosis (probands), their affected and unaffected siblings, and healthy controls, as described previously (26). Data were collected at two centers: VU Amsterdam (Amsterdam, the Netherlands) and Radboudumc (Nijmegen, the Netherlands). After a mean follow-up period of 5.9 years (SD = 0.6 years), all W1 participants were invited for follow-up measurement. This second assessment wave (NeuroIMAGE1 [W2]) followed a phenotypic protocol similar to that of W1 but with the additional acquisition of MRI brain scans (25). A third assessment (NeuroIMAGE2 [W3]) occurred only in Nijmegen after approximately 3.7 years (SD = 0.6 years) and followed the same protocol as that of W2.

The sample for our current analyses (summarized in Table 1) includes all individuals from W2 who had DWI scans that passed all quality control (n = 570). We additionally included participants who had been newly recruited as part of W3 and thus had data available from only 1 wave (n = 84 after all quality control). There were thus 654 participants from 366 families in total in the current analysis (age range, 7.72–28.59 years; mean age = 17.41 years). Of these, 322 were unaffected, 258 had a current diagnosis of ADHD, and 74 had a diagnosis of subthreshold ADHD at the first MRI acquisition time, as defined below. There were no differences on measures of ADHD severity (p = .941), age (p = .254), and sex (p = .165) between subjects in the current analysis and the whole W2 sample (n = 1085), including those who did not have available MRI data.

Table 1. Demographic and Clinical Characteristics of the ADHD Affected, Subthreshold, and Unaffected Groups Based on Participants' Diagnosis at the Time of Magnetic Resonance Imaging Acquisition

	Affected Group (n = 258)	Subthreshold Group (n = 74)	Unaffected Group (n = 322)	Test Statistic	p
Age, Years, Mean (SD)	17.4 (3.6)	18.2 (3.6)	17.2 (3.7)	$F_{1,658} = 0.76$	.38
IQ Estimate, Mean (SD)	95.1 (16.0)	102.2 (13.5)	104.3 (14.9)	$F_{2,653} = 23.9$	$<10^{-10}$
Right-Handedness, n (%)	219 (85%)	61 (82%)	276 (86%)	$\chi^2_4 = 1.1$	.89
Sex, Female, n (%)	76 (30%)	31 (42%)	170 (53%)	$\chi^2_2 = 34.6$	$<10^{-8}$
Scan Site Nijmegen, n (%)	148 (57%)	44 (59%)	167 (52%)	$\chi^2_2 = 5.1$	.08
Head Motion, Mean (SD)	0.76 (1.1)	0.75 (1.3)	0.59 (0.4)	$F_{2,655} = 3.1$	.05
Diagnosed Ever, Yes, n (%)	258 (100%)	24 (32%)	20 (6.2%)		
CPRS HI + IA, Mean (SD)	22.4 (12.1)	11.1 (9.6)	4.3 (4.9)		
CPRS HI, Mean (SD)	9.6 (6.5)	3.7 (4.5)	1.3 (2.1)		
CPRS IA, Mean (SD)	14.2 (7.1)	7.2 (5.6)	2.9 (3.5)		
K-SADS-PL HI, Mean (SD)	5.2 (2.5)	2.8 (2.0)	2.1 (2.0)		
K-SADS-PL IA, Mean (SD)	7.0 (1.4)	4.7 (0.8)	6.0 (2.1)		
Impaired, Yes, n (%)	252 (98%)	35 (47%)	12 (3.7%)		
Duration Medication Use, Days, Mean (SD)[a]	1413 (332)	645 (1111)	46 (332)		
History of Medication Use, Yes, n (%)[a]	202 (78%)	27 (36%)	10 (3.1%)		
Comorbidity, n (%)[b]					
Conduct disorder	12 (4.7%)	1 (1.4%)	0 (0%)	$\chi^2_2 = 1.3$	.53
Major depression	2 (0.8%)	0 (0%)	1 (0.3%)	$\chi^2_2 = 1.3$	.52
Oppositional defiant disorder	76 (30%)	6 (8.1%)	5 (1.6%)	$\chi^2_2 = 93.5$	$<10^{-15}$
Substance Use Ever, n (%)[c]					
Alcohol	52 (20%)	13 (18%)	51 (16%)	$\chi^2_2 = 1.7$	.42
Tobacco	125 (48%)	27 (36%)	102 (32%)	$\chi^2_2 = 16.8$	.0002
Cannabis or hash	72 (28%)	18 (24%)	57 (18%)	$\chi^2_2 = 8.9$	.01
Other	26 (10%)	7 (9.5%)	15 (4.7%)	$\chi^2_2 = 6.9$	.03

Demographic between-group differences were tested using F tests for continuous variables and χ^2 tests for categorical variables. Totals are for all participants who were included in the final sample, after all quality control. Medications were Ritalin (methylphenidate), Concerta (methylphenidate), Strattera (atomoxetine), and any other ADHD medication.

ADHD, attention-deficit/hyperactivity disorder; CPRS, Conners' Parent Rating Scale; HI, hyperactivity-impulsivity; IA, inattention; K-SADS-PL, Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime Version.

[a]The majority of patients were taking prescription medication for ADHD, mostly methylphenidate or atomoxetine. Duration of medication use was recorded as the cumulative number of days of use, while the history of medication use was recorded as whether or not the participant had ever taken ADHD medication. Further details on medication use in our sample is available in previous work (60,61).

[b]History of comorbid disorders was screened for via the K-SADS-PL semi-structured interview (27,62). For children <12 years of age, the child's parents or researchers assisted in the completion of the self-report questionnaires. Participants with elevated scores on one or more of the K-SADS screening questions were further asked to complete a full supplement for each disorder. The final diagnosis was based on DSM-IV criteria of each disorder.

[c]Substance use at any point before assessment was recorded through self-report (63–65).

Clinical Assessments

A full description of the clinical assessments in our sample is available in previous work (25). ADHD diagnosis, clinical impairment, and symptom severity scores for IA and HI were determined through the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime Version and the Conners' Parent Rating Scale (CPRS) questionnaires at W1, W2, and W3 (27,28). An algorithm was applied to combine information from clinician interview and questionnaires, as detailed previously (25). A participant was diagnosed with ADHD according to DSM-IV criteria (if he/she had ≥6 IA and/or ≥6 HI symptoms for participants <18 years of age; or ≥5 symptoms for participants ≥18 years of age), causing functional impairment at home, at school or work, or in social settings (29). Unaffected participants (including unaffected siblings and unrelated controls) were required to have a score of ≤3 in both symptom dimensions (≤2 symptoms for participants ≥18 years of age). Participants who fulfilled criteria for neither ADHD nor unaffected status were classified as subthreshold ADHD. The CPRS questionnaire was used to assess symptom severity because of its comprehensive symptom coverage for ADHD and psychometric properties more suitable for dimensional analyses. Multiple-setting clinical impairment was investigated separately, defined as impairment in at least 2 of the 3 domains according to the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime Version interview: school/work, home, and social.

Imaging Acquisition and Analysis

MRI data were acquired with either a 1.5T MAGNETOM Sonata or a 1.5T AVANTO scanner (Siemens, Erlangen, Germany): twice-refocused pulsed gradient spin echo echo-planar imaging; 60 diffusion-weighted directions; b-factor 1000 s/mm²;

5 non–diffusion-weighted images; interleaved slice acquisition; echo time/repetition time = 97 ms/8500 ms; GRAPPA (generalized autocalibrating partially parallel acquisition) acceleration 2; phase full Fourier; voxel size 2.0 × 2.0 × 2.2 mm. Both scanners were equipped with the same 8-channel phased-array head coil. More details of the T1-weighted and DWI data acquisition have been described previously (25). DWI images were preprocessed and included motion and eddy-current corrections (25,30). Diffusion tensor eigenvectors, eigenvalues, and FA were then calculated for each voxel (31). Bedpostx (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#BEDPOSTX) was applied with a 2-fiber model to estimate the distributions of the diffusion parameters for probabilistic tractography (32).

We then applied TRACULA (Tracts Constrained by Underlying Anatomy) (http://surfer.nmr.mgh.harvard.edu/fswiki/Tracula) (24), a FreeSurfer toolbox, to delineate 18 major WM tracts (Figure 1). TRACULA is a method for the automated reconstruction of major WM pathways based on an earlier well-known global probabilistic approach (33). TRACULA extends this algorithm by incorporating anatomical knowledge in the prior probability function so that the final segmented tract is the best fit not only given the observed diffusion data within each subject, but also given its similarity to the known tract anatomy in relation to gray matter segmentations from FreeSurfer.

We used FreeSurfer 5.3 to define cortical and subcortical regions in the T1-weighted images of each individual (34). FreeSurfer segmentations were checked for quality based on a modified version of the ENIGMA Protocol 2.0 (http://enigma.ini.usc.edu/protocols/imaging-protocols/), resulting in 22 exclusions. Next, trac-all was run in TRACULA to segment all of the abovementioned tracts in native space. We visually checked the anatomical accuracy of each subject's tract segmentation output, resulting in 7 exclusions (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeviewGuide). Figure 1 illustrates TRACULA's segmentation output in a single healthy control subject. Finally, each participant's scan was registered to Montreal Neurological Institute space for analyses of FA at each location along the tract.

Statistical Analyses

All statistical analyses were performed in R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). We investigated 4 types of effects and tested each separately as a fixed factor: 1) current ADHD diagnosis at the time of first MRI acquisition (state), 2) having ever been diagnosed with ADHD (trait), 3) clinical impairment, and 4) total symptom scores on HI and IA dimensions separately. In categorical analyses 1 and 2, the subthreshold group was excluded. In analysis 1, 322 participants were unaffected and 258 were affected with ADHD. For analysis 2, 312 participants had not been diagnosed with ADHD by the time of scan (never), while 292 had been diagnosed by the time of scan (ever).

For all analyses, a stepwise approach was taken, in which first global effects across all tracts and interactions with tract were tested. Only if we found a significant overall effect or a significant interaction effect with tract did we examine the effect of the independent variable in question on FA in individual tracts. For these tract-specific analyses, p values were Bonferroni corrected for the number of tracts, reported as family-wise error p (p_{FWE}) ($p_{FWE} = p \times 18$). For both global and by-tract analyses, we applied linear mixed-effects regression models (R package "lme4" version 1.1-21). All analyses incorporated age, sex, MRI acquisition site, assessment wave, and head motion (framewise displacement) as fixed effects and family membership as a random effect. Global models also included tract as a fixed effect and subject as a random effect. See Table S7 for a summary of our models.

If any tract was significant in the previous analyses, we performed a pointwise comparison of FA per voxel for every location along the tract.
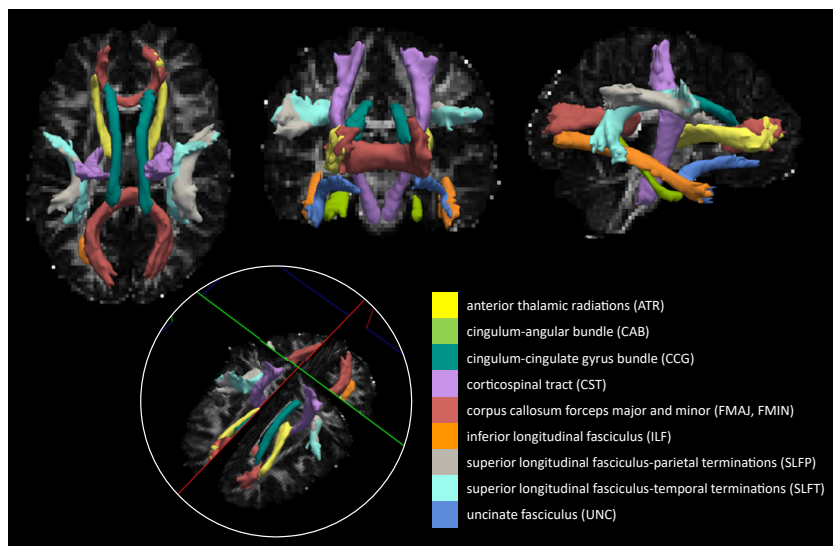

Figure 1. Example pathway reconstruction and merged 4-dimensional volume output of TRACULA in a healthy control subject. All 18 white matter tracts (8 bilateral and 2 interhemispheric) are displayed at 20% of their maximum probability distribution threshold as an isosurface over the subject's FreeSurfer segmentation, overlain on the subject's diffusion data, and displayed from axial, coronal, and sagittal views.

anterior thalamic radiations (ATR)
cingulum-angular bundle (CAB)
cingulum-cingulate gyrus bundle (CCG)
corticospinal tract (CST)
corpus callosum forceps major and minor (FMAJ, FMIN)
inferior longitudinal fasciculus (ILF)
superior longitudinal fasciculus-parietal terminations (SLFP)
superior longitudinal fasciculus-temporal terminations (SLFT)
uncinate fasciculus (UNC)

In our post hoc analyses, we investigated effects of medication use by separately adding use of any ADHD medication as a binary factor and then as a continuous factor. Potential effects of IQ, substance use, and major comorbidities were also separately analyzed through the addition of each variable as a fixed factor.

RESULTS

State and Trait Effects of ADHD Diagnosis

There was no association of ADHD state or ADHD trait with FA, globally across all tracts (Table 2). Both ADHD state and trait showed highly significant interaction effects with tract ($p <$ .0006), which led us to further examine FA differences by tract (tract-specific models). However, there were no significant effects on FA for any specific tract; in fact, all uncorrected p values were >.05 (Tables S1 and S2).

Supplementary analyses including subthreshold participants showed nonsignificant effects of state or trait on global and tract-specific FA, though there were significant tract–interaction effects ($p <$ .0005) (Table S8, S9, and S10). There were also no significant main or tract-by-group interaction effects for each of the DSM-V presentation subtypes

Table 2. All Global Model Analyses

	t	df	Standardized β	p	Tract Interaction p
State	−0.924	489	−.011	.356	.000537[a]
Trait	−0.513	584	−.006	.608	.000003[a]
Impairment	−1.337	571	−.016	.182	.000020[a]
CPRS HI + IA	−2.280	567	−.027	.023[a]	.000140[a]
CPRS HI	−2.160	556	−.026	.031[a]	.000017[a]
CPRS IA	−2.174	564	−.026	.030[a]	.006162[a]

Associated t values, degrees of freedom, standardized beta coefficients, uncorrected p values, and interaction with tract p values for each overall fractional anisotropy analysis.

CPRS, Conners' Parent Rating Scale; HI, hyperactivity-impulsivity; IA, inattention.

[a]Significant global model for CPRS symptom dimension scores and all tract interaction effects.

separately (HI, IA, combined) on FA (Table S11). We also found no difference in global FA between unaffected siblings of affected individuals and unaffected controls with no affected sibling. Though there was a significant tract
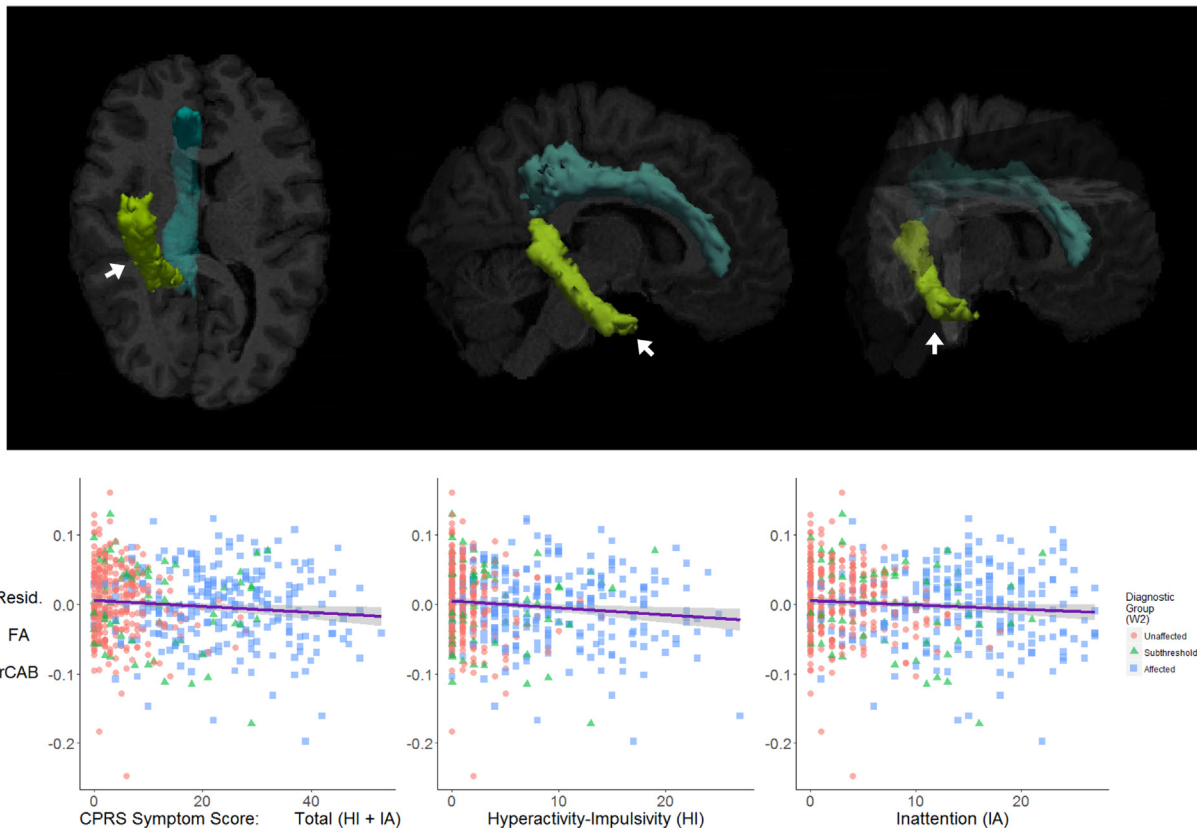

Figure 2. Tract-specific right cingulum angular bundle (rCAB) mean fractional anisotropy (FA) and symptom score. (Top panel) TRACULA (Tracts Constrained by Underlying Anatomy) reconstruction in a healthy control of the rCAB in green and indicated by white arrows, from inferior (left), right (middle), and ventral anterior (right) views, respectively. The cingulum cingulate gyrus bundle is shown in blue for reference. (Bottom panel) Scatterplots with regression lines (95% confidence intervals) of the association between each dimension score (combined, hyperactivity-impulsivity [HI], and inattention [IA]) and the residuals (Resid.) of rCAB mean FA. Data points are grouped according to each participant's diagnosis at wave 2 (W2). Mean FA in the rCAB had a negative association with HI symptom score but not with IA symptom score. See Table S4 for associated statistics. CPRS, Conners' Parent Rating Scale.
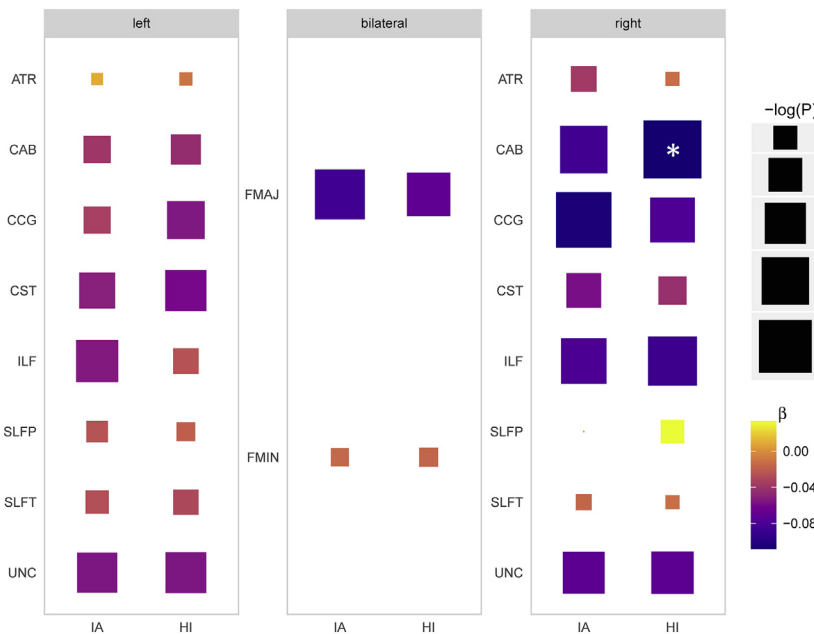
Figure 3. All tract-specific models for the effect of Conners' Parent Rating Scale symptom dimension (inattention [IA] and hyperactivity-impulsivity [HI]) on fractional anisotropy. Uncorrected p values and standardized β coefficients: negative log of the p values are represented by size so that more significant values are larger; more negative β coefficients are displayed in darker color; the only significant tract-specific model is marked by an asterisk. See Table S4 for associated statistics. ATR, anterior thalamic radiations; CAB, cingulum angular bundle; CCG, cingulum cingulate gyrus bundle; CST, corticospinal tract; FMAJ, corpus callosum forceps major; FMIN, corpus callosum forceps minor; ILF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus parietal terminations; SLFT, superior longitudinal fasciculus temporal terminations; UNC, uncinate fasciculus.

interaction (p = .0005), there were no significant tract-specific models (Table S7).

Clinical Impairment

Our global model for the association between FA and impairment resulted in no association with impairment and an interaction effect with tract (p = .00002). No tracts had a significant association of FA with impairment (Table S3).

Continuous Symptom Scores

The global models indicated main effects of IA and HI CPRS scores (p = .030 and p = .031, respectively) and again significant interaction effects with tract (both $p < .007$) (Table 2). Tract-specific models for HI CPRS score showed a negative association between the right cingulum angular bundle (rCAB) FA and HI ($t_{632} = -3.04$, $p_{FWE} = .045$). Figure 2 provides a closer inspection of this effect in the rCAB for each symptom dimension against FA. Other tracts did not show associations

between FA and either symptom dimension at Bonferroni-corrected significance levels (Figure 3 and Table S4).

Pointwise Comparison of FA Along rCAB

The effect of IA and HI scores on FA was relatively equally distributed along the length of the tract, with slightly larger negative effects at the posterior end compared with at the anterior end (Figure 4). There is no particular rCAB area or voxel that contributed significantly more than others to the association between FA and HI score, nor to that of FA and IA score (Table S5). Exploratory analyses of effects in all other tracts also revealed no significant differences (Figure S1).

Post Hoc Analyses

Details and correlations between global and rCAB FA and medication use, comorbid disorders, substance use, and IQ are presented in Table 3. Days of medication use was nominally associated with rCAB FA (p = .042). Therefore, to test for
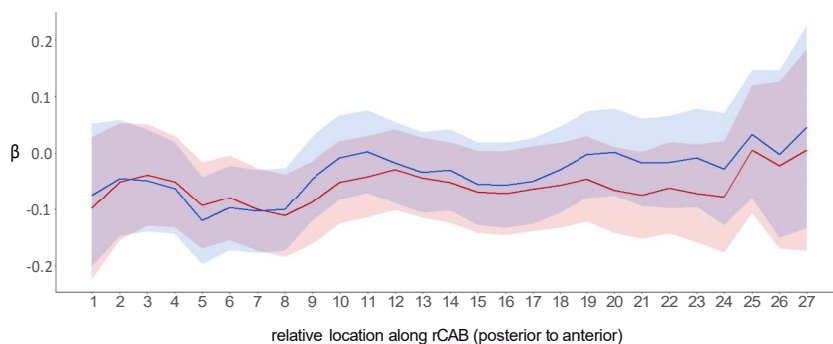

Figure 4. Pointwise comparison of fractional anisotropy (FA) along the right cingulum angular bundle (rCAB). Colored lines show the standardized β coefficients (95% confidence intervals) of the associations between FA along the length of the rCAB and the symptom score, grouped by symptom dimension, shown from posterior to anterior ends of the tract. β coefficients of FA associations with the hyperactivity-impulsivity symptom score are in red, and those with inattention are in blue for each of the 27 cross-sections along the standard-space tract spline. Toward each endpoint of the tract, fewer participants contributed FA data to the analysis, reflected in wider confidence intervals at the tract ends. See Table S5 for associated statistics.

relative location along rCAB (posterior to anterior)

Table 3. Post Hoc Analyses

	Global FA			Tract-Specific rCAB FA		
Variable	Standardized β	t	p	Standardized β	t	p
Medication Use						
Binary (yes or no)	−.003	−0.206	.837	−.033	−0.845	.399
Continuous, days	−.010	−0.803	.422	−.078	−2.039	.042[a]
Comorbidities (Yes or No)						
Conduct disorder	−.037	−0.714	.480	−.004	−0.116	.908
Major depression	.095	1.975	.051	−.018	−0.512	.609
Oppositional defiant disorder	−.016	−1.352	.177	−.059	−1.626	.105
Substance Use (Yes or No)						
Alcohol	−.003	−0.211	.833	−.005	−0.142	.887
Tobacco	.009	0.660	.510	.010	0.231	.818
Cannabis or hash	.002	0.118	.906	.052	1.252	.211
Other drugs	−.010	−0.719	.473	−.012	−0.313	.754
IQ Estimate	−.010	−0.837	.403	.012	0.315	.753

The standardized β coefficients, associated t values, and uncorrected p values for the regression of medication use, comorbidities, and drug use until the date of magnetic resonance imaging scan against global and rCAB FA. We found a negative effect of total duration of medication use as a continuous variable on FA but not history of medication use as a binary factor. No other factors had a significant effect on either global or rCAB FA.

FA, fractional anisotropy; rCAB, right cingulum angular bundle.

[a]Significant effect on FA in rCAB.

potential confounding effects of medication use duration, we added it as a covariate to the previously significant model of HI on FA in the rCAB. When medication use duration was included as a covariate, the effect of HI was no longer significant at our Bonferroni-corrected significance level (t_{570} = −2.207, p = .028), but neither was the effect of medication itself (t_{570} = −1.223, p = .222). Medication use and HI symptom scores were highly collinear, given a correlation when cases and controls were pooled (Spearman's ρ = .661). Medication use did not have an interaction effect with HI scores (p > .069).

Head motion, age, and sex were already included as covariates in all models. There were no significant main or interaction effects of any of these variables with any independent variable of interest on FA for all analyses reported above. Although affected and subthreshold individuals displayed greater head motion than those who were unaffected, this difference was not significant (Table 1), and there was never an interaction effect with motion in all analyses.

DISCUSSION

We performed a large, systematic analysis of ADHD clinical measures with WM microstructure using automated tractography. The presence of significant interactions with tract indicates that for all ADHD-related variables tested, ADHD's effect on FA varies across the different WM tracts. However, we did not find any evidence for FA reductions or increases in association with ADHD diagnosis, neither as a trait measure nor as a state measure, nor with impairment, across 18 major WM tracts. In contrast, regarding the HI symptom domain as a dimensional measure, our results showed reduced FA in the temporal portion of the cingulum bundle, or rCAB. Hence, our findings here suggest that continuous measures of current

symptom severity state may be more sensitive to differences in FA in association with ADHD than are categorical clinical measures.

The cingulum has been previously implicated in voxel-based studies of ADHD, but with mixed exact locations and directions of effects (2,35,36). This may be due to differences in DWI analyses, wherein the cingulum is not easily delineated by various analytic methods. Only some connections encompass the entire length of the tract, and discrete subdivisions of the cingulum display distinct FA measures at different medial-lateral positions within the bundle, indicating qualitative changes along the length of the tract (35–37). The present separation of the CAB from its dorsal counterpart may have provided greater resolution for identifying associations that were heretofore difficult to detect or were manifested differently. Moreover, our rCAB pointwise analysis revealed that IA and HI symptom effects on FA are comparable for all voxels, which indicates that our result was driven by a relatively subtle effect across the entire tract—an effect that could be more challenging to detect with voxel-based or less sophisticated tractography methods.

The CAB links the posterior default mode network (DMN) and the medial temporal lobe. Aberrant functional connectivity involving the DMN is one of the most consistent neuroimaging characteristics of ADHD (38–42). Greater severity of HI and IA have also been associated with decreased DMN connectivity (43,44). The DMN is characterized by increased activation during rest and mind wandering and has also been associated with emotional lability (45–51). Mind wandering has been associated with emotional lability and greater ADHD symptom severity (52). Our finding of reduced FA in the rCAB could speculatively be an anatomical substrate of the frequently observed altered DMN functional connectivity in ADHD, and the associated emotional problems and increased mind

wandering that may stem from aberrant activation in the DMN and its connections with the medial temporal lobe.

Given the current largest DWI ADHD sample yet and our use of a validated robust global probabilistic tractography method, the persistence of null results in association with ADHD diagnosis is noteworthy. Unlike most case-control studies, we had an advantage in that we were able to test current diagnostic status, as well as previous (usually unknown) history of diagnosis. Yet, we found no indication of an effect for either a trait or state on WM microstructure. This does not necessarily mean that WM plays no role in ADHD remission or persistence over time; future longitudinal studies can better address this as they can account for interindividual differences in clinical severity and brain features at baseline. Similar to diagnosis, we did not find an association between FA and impairment, which corroborates our earlier supposition that symptom severity neither directly nor strongly maps onto impairment. Explanations may be that impairment is partly context dependent (e.g., a supportive structured environment may lead to less hindrance from ADHD symptoms, as opposed to a chaotic unsafe environment), related to compensatory skills (e.g., intelligence or executive skills), and/or to possible comorbid symptoms.

We can further speculate as to why our analyses did not generally replicate the rather large literature reporting WM alterations related to ADHD. Our participants were adolescents; thus, our negative finding may imply WM case-control differences attenuate with age, similar to gray matter (53). However, a systematic review of DWI studies does not indicate that WM alterations are found more in younger populations (3). Perhaps the 1.5T field strength was not enough to detect our effects of interest, as opposed to 3T scanners that are more widely used today. Nonetheless, a systematic review of DWI studies did not indicate that 3T scanners are more likely to produce significant case-control differences in ADHD (3). Head motion can produce spurious DWI findings, which is of particular concern regarding ADHD, given that HI is associated with greater motion (54,55). A previous TRACULA analysis of group differences in DWI measures demonstrated that several tracts, including the rCAB, had greater group differences in DWI measures when group differences in head motion were higher (55). Until recently, many DWI studies of ADHD did not examine group differences in head motion, and similar to our categorical results here, most studies that reported no case-control difference in motion also had null results (3). All of our analyses included head motion as a covariate, and each model was checked for interaction effects with head motion.

Days of medication use was negatively associated with rCAB FA and, when added into our rCAB model, resulted in a loss of the main effect of HI score on FA. This limitation is not surprising, given that—especially when cases and controls were pooled—ADHD medication use and symptom score were highly correlated. High levels of collinearity between medication and symptom severity means that, within the context of this study design, we cannot clearly separate these effects. In contrast to our observations here, other studies have shown that methylphenidate treatment is associated with higher global FA, while other more suitably designed DTI studies that specifically investigated medication effects in ADHD patients did not find confounding effects of medication use on FA (53,56,57). The attenuated significance of both medication and HI symptoms when included in the same model tentatively supports an effect of ADHD symptomatology in combination with a secondary effect of medication use—merely owing to higher medication use by those with more symptoms.

Finally, we must note that the physiological interpretation of DWI findings remains somewhat speculative (15,58). For example, in a single fiber bundle, decreased FA may represent myelin breakdown or reduced axonal integrity, whereas in regions with crossing fibers, it may represent increased neuronal branching and could, as such, even indicate increased structural connectivity. Hence, we must be cautious in interpreting our findings in terms of specific neurobiological mechanisms. In contrast to many previous studies that used tract-based spatial statistics or other voxel-based methods, we used tractography. This allows locating any FA differences to fiber tracts with known anatomy, which aids in relating it to brain networks and brain function. In addition, on the one hand, tractography allows for more intersubject variation in the shape and size of fibers and the total brain, without affecting the FA values within the voxels. On the other hand, tractography is less sensitive to the very subtle but spatially consistent effects that are often reported using tract-based spatial statistics in combination with threshold-free cluster enhancement (59). Thus, differences in spatial location and extent between our study and previous DWI studies in ADHD should be interpreted bearing in mind these methodological choices.

Conclusions

In conclusion, to our knowledge, this is the first time that global probabilistic tractography has been applied to an ADHD DWI dataset of this size. Using TRACULA allowed for the automatic, simultaneous extraction of FA measures from hundreds of subjects. In line with previous data, we provide further evidence that accentuates the complexity of this disorder and complements information from case-control studies. We found that FA is associated with symptom dimension scores but not with categorical diagnostic ADHD measures. We conclude that associations of FA with ADHD may be more subtle than was previously thought, and that the rCAB may be more involved in the symptoms of ADHD than was previously thought.

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