Hyperactivity-impulsivity in ADHD is associated with white matter microstructure in the cingulum's angular bundle

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Abstract

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 microstructure, measured by diffusion-weighted imaging (DWI) and quantified by fractional anisotropy (FA). In the largest DWI analysis of ADHD to date, we systematically investigated if FA is associated with: current and lifetime diagnosis, categorical diagnosis and continuous symptom measures, and impairment in daily life.

DWI data were obtained from 654 participants (322 unaffected, 258 affected, 74 subthreshold; 7-29 years of age). For each subject, we applied automated global probabilistic tractography with TRACULA on 18 major white matter pathways and linear mixed effects regression models to examine associations with overall brain and tract-specific FA.

There was no significant association of FA with current diagnosis or history of ADHD diagnosis, or impairment. Lower FA was significantly associated with higher ADHD symptom severity in the right cingulum's angular bundle (rCAB; P=0.051), and this was mainly driven by hyperactivity-impulsivity symptoms (P=0.033).

This is the first time global probabilistic tractography has been applied to an ADHD DWI dataset of this size. Our findings suggest that continuous symptom measures may be more sensitive to FA differences in association with ADHD than diagnostic categories. The rCAB may play an important role in hyperactivity and impulsivity in ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age-inappropriate levels of inattention (AD) and/or hyperactivity-impulsivity (HD). Approximately 5% of children worldwide are diagnosed with ADHD and symptoms persist into adolescence and adulthood in 55-75% of cases, depending on the diagnostic criteria used (Faraone et al., 2006; Willcutt, 2012). Using diffusion-weighted imaging (DWI), alterations in white matter microstructural properties have been reported in patients with ADHD (Aoki et al., 2018; Francx et al.,

2016, 2015a, 2015b; Shaw et al., 2015; Sudre et al., 2018; van Ewijk et al., 2014, 2012). However, generally limited sample sizes and methodological differences between studies contribute to inconsistencies in the locations and directions of findings thus far. The predominant case-control design of previous studies leaves several unanswered questions that are critical for clinical impact. Here, we applied automated tractography to a large, longitudinal cohort of ADHD patients. We systematically investigated whether white matter 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.

DWI measures the magnitude and direction of water diffusion, which in white matter reflects the underlying organization of axons and their surrounding myelin (Chang et al., 2017; Mollink et al., 2017; Seehaus et al., 2015). 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 the surrounding myelin sheath (Beaulieu, 2002; Winston, 2012). To date, findings from DWI ADHD case-control studies have been largely mixed. With tract-based spatial statistics (TBSS), lower FA in ADHD has been found in fronto-occipital fasciculi, the right superior longitudinal fasciculus and bilateral orbitofrontal areas; yet, both reduced and elevated FA have been reported in the corpus callosum, fronto-occipital fasciculi, and cingulum (Aoki et al., 2018). Many case-control studies show some differences in white matter microstructure 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, as a neurodevelopmental disorder, ADHD has an approximate 50% remission rate as children grow up, as well as general fluctuations in symptom severity and impairment over time (Faraone et al., 2006). Typical case-control designs cannot disentangle effects associated with ADHD as a stable lifetime trait and ADHD as a current state. A better understanding of this difference and its dynamics has implications for assumptions behind genetic liability for ADHD and for the plastic nature of the neural mechanisms underlying ADHD, including their potential plasticity and receptiveness to treatment. Here, we refer to differences based on patients' current diagnoses as "state" effects, and to differences ever-affected individuals regardless of current diagnosis as "trait" effects. Trait effects remain identifiable in remittent patients, pointing to the possibility that diagnosis of ADHD at any point leaves an indelible 'mark' on white matter that persists throughout life, regardless of the disorder's progression. Decreased FA has been found as a trait effect of ADHD in right corona radiata, superior longitudinal fasciculus, left posterior thalamic radiation, internal capsule, and sagittal stratum, while at other times, no ADHD trait effects have been found at all (Cortese et al., 2013; Shaw et al., 2015). Thus, the evidence of state- versus trait-effects on white matter remains divided; larger sample sizes combined with sophisticated DWI analytical techniques may clarify these previous findings.

ADHD symptoms are continually distributed throughout the population, and the boundary between those with and without the disorder is ill-defined (Coghill and Sonuga-barke, 2012; Haslam et al., 2006; Marcus and Barry, 2011). Considering a continuous variable of symptom severity, rather than a categorical diagnosis, could increase power to detect related cognitive processes and brain traits that are also continuously distributed. We often overlook the possibility that non-clinical "control" participants may also exhibit ADHD characteristics and that within patient groups there is considerable variation in symptom severity. Dimensional analyses allow for modeling of the entire ADHD spectrum (Lahey and Willcutt, 2010). Generally, DWI studies that have applied dimensional analyses have been inconsistent in terms of anatomical location, and counterintuitively indicate that, within the patient population, increased symptom severity ratings are associated with higher FA (Francx et al., 2015b; van Ewijk et al., 2014; Wu et al., 2017). Given that the categorical diagnosis of ADHD has generally been associated with reduced FA, a more in-depth study of these effects is warranted.

The sole presence of (sufficient) symptoms of AD or HD 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 important factor for translational impact on the quality of life of patients. Impairment was once found to be predictive of emotional lability in ADHD, independent of symptom severity (Skirrow and Asherson, 2013). MRI studies that considered clinical impairment as a separate factor, independent of diagnosis or symptom severity, are scarce to date. The implications of impairment in diagnosis and daily life, as well as the paucity of impairment-related studies heretofore—especially with regards to FA in a large study sample—underscore the need for further evaluation of impairment and its structural basis in the brain.

All of the aforementioned DWI studies in ADHD have stratified patients, outcomes, and analyses in a variety of ways: state vs. trait, symptom dimension vs. diagnostic category, impairment, et cetera. Possibly as a consequence of this, results from DWI analyses have been perplexing in the anatomical locations of white matter differences. An additional origin of discrepancies between studies may be found in methodological differences. The use of voxel-wise analyses (e.g. TBSS or tractography) in the presence of crossing fibers and anatomical differences in tract width and shape, can potentially lead to ambiguity in the anatomical location of DWI findings. In addition, residual effects of head motion after realignment tend to be associated with the main DWI outcome measures, but are not always accounted for statistically (Aoki et al., 2018). In an effort to improve large dataset analysis in a data-driven manner—without *a priori* hypotheses—we applied an automated tractography method to one of the largest cohorts of ADHD patients and healthy controls. Previous tractography methods required user interaction (e.g. manually draw regions of interest or set thresholds for path angle and length), *a priori* selection of tracts, and employed local tractography (Yendiki et al., 2011). In contrast, our current study applies probabilistic global tractography in combination with anatomical knowledge of the tract's location and shape, allowing fully automated tractography of all major white matter tracts. Additionally, global tractography is less sensitive to localized regions of high uncertainty (e.g. areas of crossing fibers) compared to other approaches. In the largest DWI analysis of ADHD to date, we investigate the relationship of white matter microstructure with lifetime and current diagnosis of ADHD, categorical and dimensional scales of current symptoms, and ADHD-related impairment.

2. Methods

2.1 Participants

A full description of the study design is available in previous work (von Rhein et al., 2015). Subjects were part of the International Multicenter ADHD Genetics (IMAGE; W1) study, which began in 2003 and included participants who were originally recruited with an ADHD diagnosis (probands), their affected and unaffected siblings, and healthy controls as described previously in Müller et al. (2011). Diagnostic, cognitive, and genetic data were collected at two centers: the VU Amsterdam and the Radboud UMC in Nijmegen. After a mean follow-up period of 5.9 years (SD=0.6), all W1 participants were invited for a follow-up measurement. This second assessment wave (W2), previously published as NeuroIMAGE, followed a phenotypic protocol similar to that of W1, but with the additional acquisition of MRI brain scans (von Rhein et al., 2015). A third assessment wave (W3), or NeuroIMAGE 2, occurred only in Nijmegen after a period of approximately 3.7 years (SD=0.6) 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 were newly recruited as part of W3 and thus had data available from only one wave (n=84 after all quality control). There were thus 654 participants in total. Of these, 322 were unaffected, 258 had a full current diagnosis of ADHD and 74 had a current diagnosis of subthreshold ADHD at the first MRI acquisition time, as defined below. There were no differences between subjects in the current analysis (654 individuals, 366 families; 322 unaffected, 258 affected, 74 subthreshold; age range: 7.72-28.59 years, mean age=17.41 years) and the whole W2 sample, including those who did not have available MRI data (n=1085) on measures of ADHD severity (p=0.941), age (p=0.254), and sex (p=0.165).

	Affected		**Subthreshold**		**Unaffected**	
	N = 258		**N = 74**		**N = 322**	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	17.4	(3.6)	18.2	(3.6)	17.2	(3.7)
IQ estimate	95.1	(16.0)	102.2	(13.5)	104.3	(14.9)
Sex (female)	30%	N = 76	42%	N = 31	53%	N = 170
Scan site (Nijmegen)	57%	N = 148	59%	N = 44	52%	N = 167
Head motion	0.76	(1.1)	0.75	(1.3)	0.59	(0.4)
CPRS ADHD	22.4	(12.1)	11.1	(9.6)	4.3	(4.9)
CPRS AD	13.4	(7.1)	7.1	(5.6)	3	(3.5)
CPRS HD	9	(6.5)	4	(4.5)	1.3	(2.1)
K-SADS-PL AD	7	(1.4)	4.7	(0.8)	6	(2.1)
K-SADS-PL HI	5.2	(2.5)	2.8	(2.0)	2.1	(2.0)
Duration medication use (days)	1413	(332)	645	(1111)	46	(332)
History of medication use (yes)	78%	N = 202	36%	N = 27	3.10%	N = 10
Comorbidity						
Anxiety disorder	0%	N = 0	1.4%	N = 1	0.9%	N = 3
CD	4.7%	N = 12	1.4%	N = 1	0%	N = 0
Major depression	0.8%	N = 2	0%	N = 0	0.3%	N = 1
ODD	29.5%	N = 76	8.1%	N = 6	1.6%	N = 5
Panic disorder	0%	N = 0	1.4%	N = 1	0%	N = 0
Substance use						
Alcohol	20%	N = 52	18%	N = 13	16%	N = 51
Tobacco	48%	N = 125	36%	N = 27	32%	N = 102
Cannabis or hash	28%	N = 72	24%	N = 18	18%	N = 57
Other	10%	N = 26	9%	N = 7	5%	N = 15

Table 1. Demographic and clinical characteristics of the ADHD affected, subthreshold, and unaffected groups, based on participants' current diagnosis at the time of the first MRI acquisition. CD: conduct disorder; ODD: oppositional defiant disorder.

2.2 Diagnostic assessment

A full description of the clinical assessments in our sample is available in previous work (von Rhein et al., 2015). ADHD categorical diagnosis, clinical impairment, and symptom dimension severity scores for AD and HD were determined through the Kiddie – Schedule for Affective Disorder and Schizophrenia Present and Lifetime Version (K-SADS-PL) and the Conner's Parent's Rating Scale (CPRS) questionnaires at W1, W2, and W3 (Conners et al., 1999; Kaufman et al., 1997). An algorithm was applied to create a combined symptom count from the interview and questionnaires, as detailed in

von Rhein et al. (2015). A participant was diagnosed with ADHD if he/she had ≥6 AD and/or ≥6 HD symptoms, as well as multiple setting impairment according to criteria described in the DSM-IV (American Psychiatric Association, 2012). All unaffected participants (including unaffected siblings and controls) were required to have a score of ≤3 in both symptom dimensions. Diagnostic criteria were adapted for participants who were ≥18 years old, so that a combined symptom count of 5 was sufficient for a diagnosis and ≤2 symptoms in both symptom dimensions resulted in an unaffected status. Participants who fulfilled criteria for neither ADHD nor unaffected status were classified as subthreshold ADHD.

The majority of patients were taking prescription medication for ADHD, mostly methylphenidate or atomoxetine. The 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 (Johnston and O'Malley, 2011). Screening for a history of comorbid disorders was done via K-SADS-PL self-report questionnaires regarding comorbid disorders (Donker et al., 2010; Kaufman et al., 1997). For children <12 years old, either the child's parents or researchers assisted in the completion of the self-report questionnaires for the child. Participants with elevated scores on one or more of the 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. Lastly, substance use at any point before assessment was recorded through self-reported alcohol use, nicotine use, and other drug use (Gavin et al., 1989; Heatherton et al., 1991; Saunders et al., 1993). All of our post-hoc analyses here included the history of any ADHD medication use, presence of comorbid disorders, and use of each substance as a separate binary factor (i.e. a response of yes or no).

2.3 Imaging acquisition and preprocessing

MRI data were acquired with either a 1.5-Tesla MAGNETOM-Sonata or a 1.5-Tesla Avanto scanner (Siemens, Erlangen, Germany). Both scanners were equipped with the same 8-channel phased-array head coil. Whole-brain, high-resolution T1-weighted anatomical images were acquired in the sagittal plane (MP-RAGE, 176 slices, acquisition matrix 256×256, voxel size 1×1×1mm; TE/TR ¼ 2.95/2730ms, TI ¼ 1000ms, FA ¼ 7°, GRAPPA-acceleration 2). Whole-brain diffusion-weighted images were collected (twice refocused PGSE EPI; 60 diffusion-weighted directions; b-factor 1000s/mm2; 5 non-diffusion-weighted images; interleaved slice acquisition; TE/TR=97/8500ms; GRAPPA-acceleration 2; phase full Fourier; voxel size 2×2×2.2mm). DWI images were realigned and corrected for residual eddy-current (SPM8; http://www.fil.ion.ucl.ac.uk/spm, London, UK) and for artefacts from head and/or cardiac motion using robust tensor modelling (PATCH; Zwiers, 2010). Diffusion tensor characteristics, including diffusion eigenvectors, eigenvalues and FA, were then calculated for each voxel (FSL 4.1.7; Behrens et al., 2003). Bedpostx was applied with a two-fiber, ball-and-stick model to estimate the distributions of the diffusion parameters and create all of the files necessary for running probabilistic tractography (Behrens et al., 2007).

2.4 Global probabilistic tractography

We applied Tracts Constrained by Underlying Anatomy (TRACULA; Yendiki et al., 2011; http://surfer.nmr.mgh.harvard.edu/fswiki/Tracula), a FreeSurfer toolbox, to delineate 18 major white matter tracts (8 bilateral and 2 interhemispheric): corticospinal tract (CST), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UNC), anterior thalamic radiations (ATR), cingulum-cingulate gyrus bundle (CCG), cingulum-angular bundle (CAB), superior longitudinal fasciculus-parietal terminations (SLFP), superior longitudinal fasciculus-temporal terminations (SLFT), corpus callosum forceps major and minor (Fmaj, Fmin). TRACULA is a method for the automated reconstruction of major white matter pathways based on the global probabilistic approach of Jbabdi et al. (2007). TRACULA extends this algorithm by incorporating anatomical knowledge in the prior probability function, so that the final

segmented tract is not only the best fit given the observed diffusion data within each subject, but also given its similarity to the known tract anatomy in relation to grey matter segmentations from FreeSurfer.

FreeSurfer 5.3 was used to automatically segment gray and white matter and define cortical and subcortical regions in the T1-weighted images of each individual (Fischl, 2012; Fischl et al., 2004, 2002). FreeSurfer segmentations were checked for quality based on a modified version of the ENIGMA Cortical Quality Control Protocol 2.0 (http://enigma.ini.usc.edu/protocols/imaging-protocols/), resulting in n=22 exclusions. Next, `trac-all` was run in TRACULA to segment all of the above-mentioned tracts in native space. We visually checked the anatomical accuracy of each subject's tract segmentation output in FreeView, resulting in n=7 exclusions (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeviewGuide). See Figure 1 for an example of TRACULA's segmentation output in a single healthy control subject. Finally, each participant's scan was registered to standard MNI space for group-level analyses of FA at each location-point along the tract.

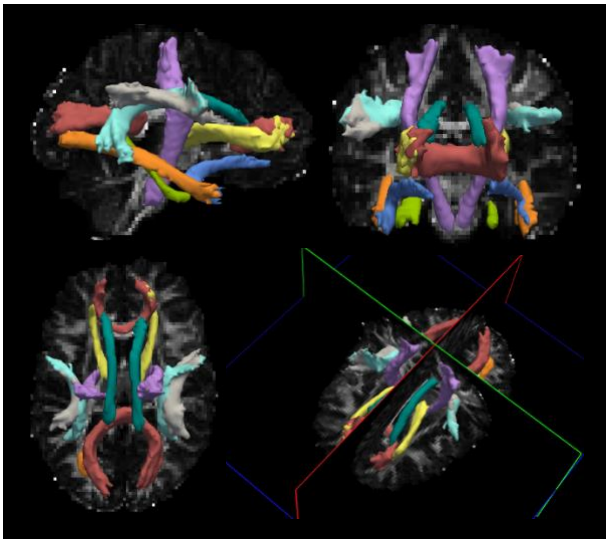

Figure 1. TRACULA pathway reconstruction and merged 4D volume output for a healthy control subject. All 18 tracts are displayed at 20% of their maximum probability distribution threshold as an isosurface over the subject's FreeSurfer segmentation: CST, ILF, UNC, ATR, CCG, CAB, SLFP, SLFT, Fmaj, Fmin.

2.5 Statistical analyses

All statistical analyses were performed in R 4.3.2 (https://cran.r-project.org/). For all analyses, the main metric of interest was mean FA within the tracts, wherein we first tested for global differences in FA (across all white matter tracts combined). If we found a significant overall effect, or a significant interaction effect with tract, we examined the strength and direction of these effects in each tract individually. For these tract-specific analyses, P-values were Bonferroni-corrected for the number of tracts, reported as P_{FWE} (P_{FWE}= P x 18). For both global and by-tract analyses, we applied linear mixed effects regression models. All analyses incorporated age, sex, MRI acquisition site, assessment wave, and head motion (framewise displacement) as fixed effects and included family identification number as a random effect. Global models also included tract as a fixed effect and subject identification number as a random effect.

We investigated 4 types of effects and tested each separately as a fixed factor using the mixed linear model: (1) current ADHD diagnosis at the time of first MRI acquisition (state), (2) having ever been

diagnosed with ADHD (trait), (3) total symptom dimension score, and scores on AD and HD domains separately, (4) clinical impairment. In the categorical analyses (1 and 2), the subthreshold group was excluded. In addition, for those tracts that were significant in the previous analyses, we performed a point-wise analysis for every location along the tract. To investigate effects of medication use, we separately added the use of any ADHD medication as a binary factor and then as a continuous factor. Potential effects of substance use and major comorbidities were also separately analyzed through the addition of each variable as a binary factor.

3. Results

3.1 State and trait effects of ADHD diagnosis

There was no association between current diagnosis (as a state) and FA, globally across all tracts. An interaction effect with tract (P=0.0001) led us to further examine FA differences by tract (tract-specific model). However, there were no significant effects of ADHD state on FA for any tract (all P>0.03 uncorrected).

The global model for the effect of history of ADHD diagnosis (as a trait) on FA also resulted in no overall effect on FA, and an interaction effect with tract (P=2.95*10^{-5}). One tract-specific model, in the right cingulum's angular bundle (rCAB), showed a trend effect for lower FA in those with a history of ADHD (P=0.008 uncorrected, t=-2.67, df=595). All other tract-specific effects were not significant (all P>0.05 uncorrected).

3.2 Continuous symptom scores

Next, our analyses deconstructed the effects of diagnostic state by first modeling the association between global FA and total CPRS score. The global model indicated no main effect of total CPRS scores, and an interaction effect with tract (P=4.84*10^{-5}). We then parsed this effect into two additional global models, which also resulted in a significant interaction effect of tract with HD score (P=7.65*10^{-8}), as well as with AD score (P=0.022).

Our tract-specific models for the total score (AD+HD) resulted in a nearly significant association between symptom score and FA in the rCAB (P_{FWE}=0.051, t=-3.0, df=591), with a significant negative association between FA in the rCAB and HD score (P_{FWE}=0.033, t=-3.13, df=593), but not with AD score (P_{FWE}=0.212, t=-2.527, df=592). Figure 2 displays our tract-specific models for each symptom dimension against FA in the rCAB. All other tract-specific models did not result in any significant association between FA and AD or HD symptom dimension scores at our Bonferroni-corrected α (all P>0.045 uncorrected, P_{FWE}>0.807).

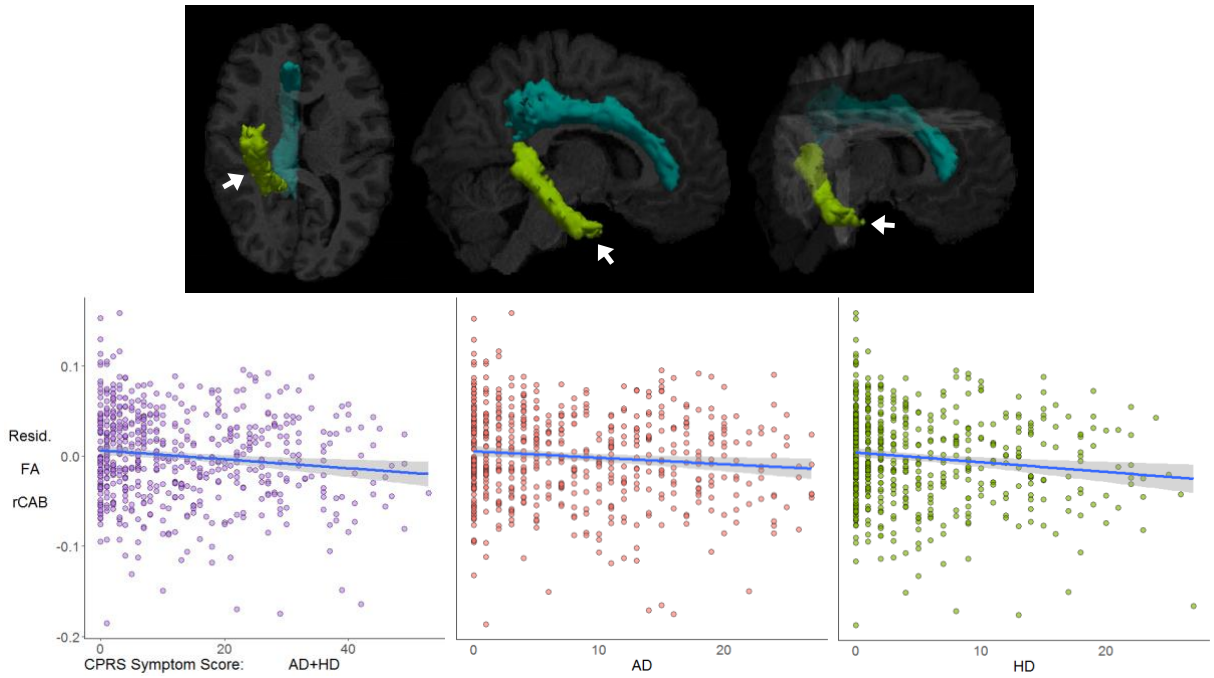

Figure 2. The top panel shows the TRACULA reconstruction of the right cingulum's angular bundle (rCAB), in green and indicated by a white arrow, from inferior, right and ventral anterior views, respectively. The cingulum's cingulate gyrus bundle is shown for reference in blue. Mean FA in the rCAB showed a negative association with total symptom scores (purple), significantly driven by HD (green), but not AD (red). Scatterplots with regression lines (and 95% confidence intervals) show the associations between each dimension score and the residuals of mean fractional anisotropy (FA) in the rCAB.

3.3 Clinical impairment

The global model for the association between FA and impairment resulted in no significant association with impairment (P=0.35), and an interaction effect with tract (P=9.91*10^{-6}). A subsequent tract-specific model indicated a trend for a negative effect of impairment in the rCAB (P=0.019 uncorrected, t=-2.35, df = 595). No other tract showed a significant association of FA with impairment (all P>0.08 uncorrected).

3.4 Point-wise comparison of FA along rCAB

Figure 3 shows the ß coefficients and confidence interval of the point-wise comparison of FA along the length of the rCAB grouped by symptom dimension. Towards each endpoint of the tract, fewer participants contributed FA data to the analysis, which is reflected in wider confidence intervals at the tract ends. The plot indicates that the effect of AD and HD scores on FA is more or less equally distributed along the length of the tract, with slightly larger effects at the posterior end compared to the anterior end. The P-values ranged from 0.006 to 0.834 uncorrected for HD score and P>0.012 for AD score. The figure also indicates that there is no particular area or voxel within the rCAB that had a significant contribution to the association between FA and HD score more than that of FA and AD score.

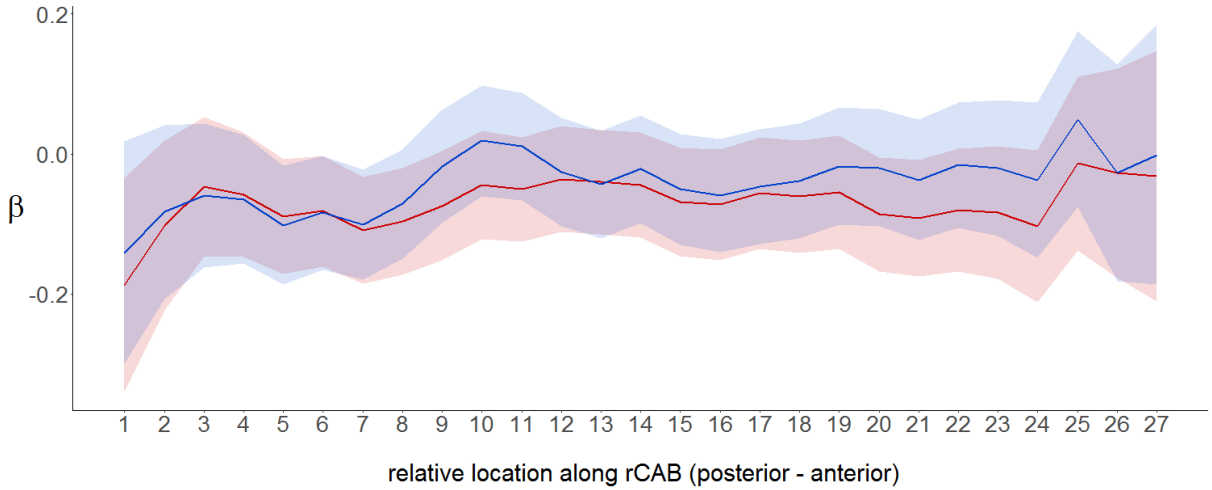

Figure 3. Lines show the standardized ß coefficients (95% confidence intervals) of the associations between FA along the rCAB and symptom score, shown from posterior to anterior ends of the tract. ß coefficients of FA associations with HD symptom score are shown in red and associations with AD are shown in blue for each cross-section along the standard-space tract spline.

3.5 Tests for potential confounds

Correlations between rCAB FA and medication use, comorbid disorders, and substance use are presented in Table 2. We found a significant effect for total duration of medication use as a continuous variable, which was negatively associated with FA. History of medication use as a binary variable showed a similar trend. Comorbid ODD was also negatively associated with FA. No other comorbid disorders or substance use had any significant effects on FA in the rCAB. Generally, with the exception of tobacco and cannabis or hash use, substance and comorbid disorders tended to be negatively associated with FA.

Because of their significant effects, duration of medication use and ODD were added as covariates to previous models that were significant. When ODD was added as a covariate, the main effect of HD score became less significant (P=0.011 uncorrected, t=-2.558, df=592), while ODD itself had no significant effect (P=0.497 uncorrected, t=-0.680, df=592). In the presence of nominally significant medication use (P=0.026 uncorrected, t=-1.835, df=520), the effect of HD was no longer significant (P=0.067 uncorrected, t=-2.226, df=517). Medication use and HD symptom scores were highly collinear, given a correlation between symptom score and medication use of Spearman's ρ=0.620. Neither medication use nor ODD diagnosis had an interaction effect with CPRS scores for AD+HD, AD, and HD (all P>0.179 uncorrected).

Head motion, age, and sex were already included as covariates in all models. There were no significant main effects or interactions of age, sex and head motion with any independent variable of interest on FA for all analyses reported above.

	std ß	**t**	**P**
Medication use binary	-0.070	-1.780	0.076
Medication use continuous	-0.121	-3.010	0.003
Anxiety disorder	-0.040	-1.140	0.255
CD	-0.004	-0.116	0.908
Major depression	-0.018	-0.512	0.609
ODD	-0.072	-2.034	0.042

Panic disorder	-0.025	-0.712	0.477
Alcohol	-0.005	-0.142	0.887
Tobacco	0.010	0.231	0.818
Cannabis or hash	0.070	1.713	0.087
Other drugs	-0.012	-0.313	0.754

Table 2. The standardized ß coefficients, associated *t* and *P* values (uncorrected) for the regression of medication use, comorbidities, and drug use until the date of scan against FA in the rCAB. CD: conduct disorder; ODD: oppositional defiant disorder.

4. Discussion

This tractography analysis provides new information on the nature, effect, and neuroanatomical location of previous findings from TBSS in a largely overlapping sample (Francx et al., 2015b; van Ewijk et al., 2014). Although FA associations with ADHD were not significant at the global level across all tracts, the consistent interaction with tract indicates that effects vary depending on the tract. Overall higher ADHD symptom scores were associated with reduced FA in the rCAB, and this was mainly driven by the HD dimension, rather than the AD dimension. When participants were grouped by current diagnosis, there were no significant differences in FA between groups. However, when subjects were pooled by lifetime diagnosis as a trait, a trend appeared in the rCAB, wherein subjects who had ADHD at any point, exhibited lower FA in the rCAB. Likewise, associations of FA with impairment at the time of scanning also resulted in a trend in the rCAB. Hence, the present tractography analyses suggest that continuous symptom measures of current symptom severity state may be more sensitive to differences in FA in association with ADHD than are categorical clinical measures.

Our results suggest that the rCAB may play an important role in ADHD. As a whole, the cingulum bundle spans the frontal, parietal, and medial temporal areas of the brain, as well as links subcortical nuclei to the cingulate gyrus (Bubb et al., 2018). FA in this prominent white matter tract has been implicated as a factor in ADHD symptom severity, as well as a marker of individual differences in neurocognitive development (Bathelt et al., 2019; Cooper et al., 2015). Additionally, a voxel-based meta-analysis of whole brain voxel-based analysis studies found that individuals with ADHD showed elevated FA in the cingulum when compared to controls; the same study also found that individuals with ADHD had lower FA compared with controls in the anterior cingulate cortex (Aoki et al., 2018).

The CAB is the ventral portion of the cingulum bundle, posteriorly beginning at the splenium of the corpus callosum and continuing medial to the inferior longitudinal fasciculus, including connections to and from hippocampal and parahippocampal regions. Our study is the first to associate FA with ADHD specifically in only the ventral (i.e. temporal or parahippocampal) portion of only the right cingulum. This may be due to differences in DWI analyses, wherein the cingulum is not always delineated in the same way by other tract reconstruction methods. Only some connections encompass the entire length of the tract and different subdivisions of the cingulum display distinct FA measures at different medial-lateral positions within the bundle, even in areas of overlap—indicating qualitative changes along the length of the tract (Bubb et al., 2018; Heilbronner and Haber, 2014; Jones et al., 2013). The CAB also consists of projections from the amygdala and thalamic nuclei, and runs close to the inferior longitudinal and uncinate fasciculi. Therefore, efforts to relate cingulum structure with cognitive or behavioral measures considerably depend on how and where the cingulum is reconstructed. Given the length and complexity of the cingulum bundle, perhaps more tract subdivisions might enhance the exposure of potential underlying associations. Similarly, the present separation of the CAB from its dorsal counterpart, in conjunction with an approach using continuous symptom dimension scores, may

have provided us with greater resolution to identify associations that were heretofore barely detectable.

Nevertheless, our point-wise analysis within the rCAB did not yield any significant differences between voxels on the effect of either AD or HD symptom score on FA; thus, suggesting that greater subdivision of this tract may not be informative in relation to ADHD. Future tractography studies should, however, strive to supplement tract-specific analyses with an inspection of if and where there are changes within a tract, which, along with crossing fibers and fibers of passage—especially in large complex axonal bundles—may impact discrete areas of a tract in distinct ways.

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 (Konrad and Eickhoff, 2010; Posner et al., 2014; Marcos-Vidal et al., 2018; van Rooij et al., 2015; Sidlauskaite et al., 2016). Greater severity of hyperactivity-impulsivity and inattention have also been associated with decreased DMN connectivity (Elton et al., 2014; von Rhein et al., 2017). The DMN is characterized by increased activation during rest and mind wandering, and has also been associated with emotional lability (Christoff et al., 2009; Fox et al., 2005; Godwin et al., 2017; Greicius et al., 2003; Martins and Mather, 2016; Mittner et al., 2016; Raichle et al., 2001). Mind wandering has been associated with emotional lability and greater ADHD symptom severity (Helfer et al., 2019). 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.

Head motion can produce spurious DWI findings, which is of particular concern regarding ADHD, given hyperactivity is associated with greater motion (García Murillo et al., 2015; Yendiki et al., 2014). Up until recently, many studies did not examine potential group differences in head motion and most studies that reported no case-control difference in motion also showed no significant results (Aoki et al., 2018). All of our analyses included head motion as a covariate and each model was checked for interaction effects with head motion. Although affected and subthreshold individuals displayed greater head motion than those who were unaffected, this difference was not significant and no interaction effects of motion were found with symptom score, diagnosis or impairment.

There are a number of limitations to this study. This was an observational nonrandomized study, in which the vast majority of ADHD participants were taking or had taken ADHD medication, and where medication use is related to clinical severity. Days of medication use was significantly negatively associated with FA and, when added into our rCAB model, resulted in a loss of the main effect of HD symptom score on FA. This is not surprising, given that—especially when patients and controls were pooled—ADHD medication use and symptom score were very highly correlated. As such it is difficult to tease apart these effects in our sample, which requires a study design that is balanced with respect to medication use and clinical severity. Since medication use explained a substantial part, but not all of the effects of symptom severity on FA, we tentatively infer that both may be associated with reduced FA in the rCAB. More in-depth, and ideally, randomized studies are warranted to determine the precise effects of medication use on white matter microstructure in relation to symptoms and impairment.

Finally, it is important to note that the physiological interpretation of DWI findings remains somewhat speculative (Beaulieu, 2002; Jones et al., 2013). 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 TBSS 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, tractography allows for more inter-subject 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 TBSS in combination with threshold-free cluster enhancement (Sprooten et al., 2016, 2013, 2011). 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.

4.1 Conclusion

In conclusion, to our knowledge, this is the first time 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. FA mapped onto symptom dimension scores, more so than other clinical measures, revealing that the rCAB may be more involved in symptom severity of ADHD than previously thought.

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