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ORIGINAL PAPER

White matter abnormalities and their impact on attentional performance in adult attention-deficit/hyperactivity disorder

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Abstract Inattention is the most important behavioral feature of adult patients with attention-deficit/hyperactivity disorder (ADHD). Neuroimaging studies in ADHD have demonstrated abnormalities primarily in the frontostriatal circuitry and were mostly conducted in children. We investigated white matter (WM) integrity in adult ADHD patients and the correlation of WM microstructure and neuropsychological parameters in 37 (21 men) never-medicated adult ADHD patients and 34 age- and gender-matched healthy controls. All subjects underwent clinical interviews, rating scales, and neuropsychological tests of attentional performance. Diffusion tensor imaging (DTI) was acquired, and 12 WM regions-of-interest (ROIs) within the attentional network were chosen. Group differences of mean fractional anisotropy (FA) and mean diffusivity (MD) values were calculated for each ROI, and patients' DTI measures were then correlated with measures of attentional performance. FA values in ADHD patients were significantly reduced in the left inferior longitudinal fasciculus (ILF), while MD values were significantly increased in ADHD patients in the frontal portion of the left frontooccipital fasciculus (IFO). In ADHD patients, MD values were negatively correlated with attentional performance in the left ILF. Our findings provide further support for disturbed frontostriatal structural connectivity and also point to an involvement of the left temporal white matter with an impact on attentional performance.

Keywords Attention-deficit/hyperactivity disorder · Diffusion tensor imaging · Fractional anisotropy · Mean diffusivity · Attention

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most frequent psychiatric disorder in childhood and adolescence with an estimated prevalence of 3–5%. In a large number of patients, ADHD persists into adulthood [18], though it has been less well studied in adults. ADHD is best characterized behaviorally as a disorder of self-regulation or executive functioning, and its clinical features include inattention, concentration deficits, hyperactivity, and impulsivity [51]. Several findings support the notion that ADHD is a dimensional disorder and the symptom severity correlates with the extent of underlying neurobiological deficits [48]. Recent research has focused on identifying the etiology of ADHD. There is evidence that the disorder is highly heritable [28] and may be associated with neurobiological deficits in the prefrontal cortex and related subcortical systems [12, 55]. Working memory and

attention deficits are suggested to be the underlying core deficits of ADHD [40].

Most neuroimaging studies of ADHD patients have been conducted in children and adolescents. A large number of imaging studies investigated volume differences with magnetic resonance imaging (MRI) measurements (for review: [52, 58]). These studies primarily demonstrated abnormalities of the frontostriatal circuitry (e.g., dorsolateral prefrontal cortex, basal ganglia, anterior cingulate) but also of other cortical regions and the cerebellum [12, 21, 52, 58]. So far, a limited number of MRI studies in adult ADHD patients have been published [25, 35, 36, 53]. Seidman et al. [53] demonstrated significantly smaller overall cortical gray matter and prefrontal and anterior cingulate cortex (ACC) volumes in adult ADHD patients. The same group also reported significant cortical thinning in ADHD in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal lobule, and the ACC [35]. Another volumetric MRI study found a significant reduction in the volume of the left orbitofrontal cortex [25].

Most functional imaging studies in ADHD patients demonstrated abnormal activation primarily in frontal cortices and the anterior cingulum [10, 16, 49, 50], supporting the hypothesis of disturbed frontostriatal connectivity. Bush et al. [9] described a lack of activation in the anterior cingulate cortex during an attentional task in adult ADHD patients, which had all been exposed to medications used in the treatment for ADHD but had undergone a washout period prior to scanning.

During the last years, magnetic resonance diffusion tensor imaging (MR-DTI) became available to investigate human brain microstructure, i.e., the integrity of white matter (WM) fiber tracts. With MR-DTI, diffusion of water molecules can be characterized by two diffusion parameters: mean diffusivity (MD), which measures the rotationally invariant magnitude of water diffusion, and fractional anisotropy (FA), which provides an index of directional selectivity of water diffusion [5]. In brain WM, myelination properties, fiber organization, axonal diameter, fiber density, the amount of fiber crossings, and the ratio of intracellular/extracellular space contribute to differences in FA and MD [5, 32, 47]. To date, only a small number of MR-DTI studies in ADHD patients have been published: A voxel-based MR-DTI analysis demonstrated decreased FA predominantly in the frontal and cerebellar WM in ADHD children [1]. Hamilton et al. [24] investigated nine WM regions-of-interest (ROIs) in 17 male children and adolescents with ADHD and 16 control subjects and found decreased FA in the superior longitudinal fasciculus (SLF) and the corticospinal tract. Casey et al. [11] showed a correlation between FA in right prefrontal fiber tracts and activity in the inferior frontal gyrus and caudate nucleus in parent–child dyads with ADHD. Makris et al. [36] investigated the cingulum bundle and SLF as parts of the attentional and executive system and reported lower FA in the right cingulum bundle and in the right SLF in adult ADHD patients.

In a voxel-based MR-DTI study, we were recently able to demonstrate impaired white matter integrity particularly in frontobasal regions in 37 never-medicated adult combined-type ADHD patients compared with 34 healthy control subjects [31]. We found reduced FA as well as higher MD bilaterally in orbitomedial prefrontal WM and in the right anterior cingulate bundle, while elevated FA was present bilaterally in temporal WM structures [31]. Measures of attention were correlated with DTI parameters in the right superior longitudinal fasciculus, whereas measures of impulsivity were correlated with FA in right orbitofrontal fiber tracts [31]. In the present region-of-interest (ROI) analysis, which was conducted prior to our voxel-based analysis of this data set (i.e., unguided by the voxel-based results), we sought to clarify whether the voxel-based findings are comparable when adopting the statistically more conservative ROI approach that is less susceptible to multiple testing. Along the line of our previously published paper, we hypothesized that impaired white matter integrity should be predominantly affected in frontobasal white matter structures.

Methods

Subjects

We investigated 37 adult ADHD patients (21 men; mean age 32.5 years, range 18–49 years) and 34 healthy control subjects (16 men; mean age 30.2 years, range 19–53 years; Table 1) as described previously in detail [31]. All patients were recruited from the outpatient clinic of the Department of Psychiatry of the University Medical Centre of the Johannes Gutenberg-University Mainz (Germany). Control subjects were recruited via local newspaper announcements. All subjects were right-handed Caucasians.

We included only patients with the combined ADHD type. Additional psychiatric disorders were excluded by clinical interviews (see below) over a period of 6 months before and a 6-month follow-up period after inclusion in the study. Other exclusion criteria were current or recent drug or alcohol abuse, any current or past psychotropic medication, and an intelligence quotient (IQ) less than 80. Written informed consent was obtained from all study participants prior to their inclusion in the study. The study has been performed in accordance with the ethical standards of the Declaration of Helsinki, and it has been

Table 1 Demographic and neuropsychological data

	ADHD patients Mean ± SD	Controls Mean ± SD	*P* value
Gender (m/f)	21/16	16/18	0.42
Age (years)	32.5 ± 10.3	30.2 ± 8.2	0.31
Education (years)	13.4 ± 3.0	13.8 ± 2.3	0.56
Smoker/non-smoker	16/21	6/28	0.02*
IQ	109.8 ± 8.7	111.4 ± 8.7	0.47
RT	373.2 ± 92.4	330.9 ± 41.1	0.03*
RT-variability	124.2 ± 48.7	81.7 ± 38.8	0.0004*
ADHD score (TOVA)	−4.4 ± 5.7	1.7 ± 2.0	3×10^{-7}*
Stroop task (number of errors)	4.0 ± 3.4	3.2 ± 3.8	0.43
WURS (25 items)	57.3 ± 18.1	18.5 ± 11.1	7.1×10^{-16}*
WURS (61 items)	106.7 ± 35.6	49.6 ± 18.7	4.4×10^{-12}*
BADDS	76.8 ± 21.1	15.8 ± 15.0	9.4×10^{-22}*

BADDS Brown Attention-Deficit Disorder Scale for Adults; *IQ* Intelligence quotient; *RT* Reaction time; *SD* Standard deviation; *TOVA* Test of variables of attention; *WURS* Wender Utah Rating Scale; * Significant group difference ($P < 0.05$, uncorrected)

approved by the Ethics Committee of the Johannes Gutenberg-University Mainz (Germany).

Control subjects were only enrolled in the study if there was no evidence for any medical or neurological illness and if there was no history for any other psychiatric DSM-IV axis I or axis II disorder including current or recent drug or alcohol abuse.

Clinical and Neuropsychological measures

DSM-IV criteria for adult ADHD were assessed with a detailed clinical interview and by adopting a German Diagnostic Interview Schedule [33]. In addition, the German version of the Wender Reimherr Adult Attention Deficit Disorder Rating Scale was used, which is based on a structured interview including 28 ADHD-related psychopathological items in 7 subcategories [43]. To examine for psychiatric comorbidity, we performed the German versions of the structured clinical interview for DSM-IV (SCID-I and SCID-II) [20, 60], the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [22], the Beck Depression Inventory (BDI) [6], and the Social Phobia and Anxiety Inventory (SPAI) [7]. Smoking status was assessed by the number of cigarettes per day and years of smoking.

In addition, the following questionnaires were completed by all participants: The Wender Utah Rating Scale (WURS) for the description of childhood behavior is considered to be a sensitive aid in the retrospective diagnosis of childhood ADHD [59]. We adopted the German version of the 61-item form of the WURS as well as the German short version (WURS-k) [42], which has been validated for clinical diagnostics [41]. Present symptomatology was tested using the Brown Attention-Deficit Disorder Scale for Adults (BADDS) [8].

All patients and control subjects also underwent a large neuropsychological test battery as described by us previously in detail [31]. IQ was measured by the Achievement Measure System (*Leistungspruefsystem*, LPS) [27], which is a common standardized German test to measure general intelligence. We adopted a short form of the LPS, which consists of six subtests [57]. Results of LPS are given in terms of IQ scores with a mean of 100 and a standard deviation of 15. Attentional functions were assessed with the test of variables of attention (TOVA) [23], which was also used to measure mean reaction time (RT) and RT variability. RT variability has been described as a sensitive measure for attentional control and is one of the most frequently reported deficits in ADHD [14]. The Stroop task was performed to test directed attention [56].

MR-DTI image acquisition

MRI investigations were performed with a conventional head-cage coil on a 1.5 Tesla system (*Vision Magnetom; Siemens, Erlangen, Germany*) with gradients of 25 mT/m, as described by us previously [4, 19]. MR-DTI images were acquired with a transversal diffusion-weighted single-shot spin-echo echo-planar–based sequence (TR/TE = 8,000 ms/100 ms, $b = 0$, and 900 mm^2/s, matrix size of 128 × 128, 5 mm slice thickness, 30% separation factor, voxel size 1.8 × 1.8 × 5.0 mm) with diffusion-sensitizing gradients shot along six non-collinear directions. At the time of the initiation of the study in 2003, it was still standard to acquire DTI data sets in six non-collinear diffusion-sensitizing gradient directions. All transversal slices were arranged parallel to the AC–PC line. At the time when the study was planned, these were standard imaging parameters.

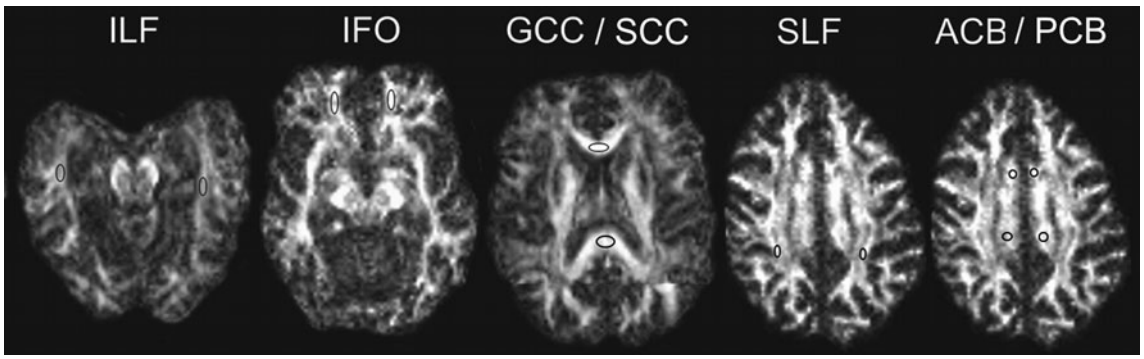

Fig. 1 Regions-of-interest on fractional anisotropy maps. *ILF* inferior longitudinal fasciculus; *IFO* inferior frontooccipital fasciculus; *GCC* genu of the corpus callosum; *SCC* splenium of the corpus callosum; *SLF* superior longitudinal fasciculus; *ACB* anterior cingulum bundle; *PCB* posterior cingulum bundle

Image processing and region-of-interest analysis

The sets with MR-DTI data were imported to a Linux x86-based workstation using DICOM, where an in-house-developed software was used to compute the diffusion tensors as described by Basser et al. [2]. The decomposition of the diffusion tensor (D) in an eigensystem was accomplished with a routine for symmetric bi-diagonalization followed by QR reduction found in GSL (*GNU Scientific Library 1.4*).

Mean diffusivity (MD), given in mm^2/s, is the mean of the diffusion tensor eigenvalues. FA is the standard deviation of eigenvalues from the MD normalized by square norm of eigenvalues [3]. FA and MD values were voxel-wise plotted as FA and MD index maps. The voxel values in the FA maps were equal to FA multiplied by a factor of 10^3. In addition, color maps encoding the orientation of main diffusivity were created for the representation of the main diffusion tensor directions. FA and MD values were measured for all patients and control subjects by one experienced and blinded investigator using the software ImageJ version 1.39a (*Wayne Rasband, National Institutes of Health, USA*) by placing regions-of-interest in the following white matter structures of the attentional network: superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior frontooccipital fasciculus (IFO), splenium and genu of the corpus callosum (SCC, GCC), anterior cingulum bundle (ACB), and posterior cingulum bundle (PCB). Since for ILF, IFO, SLF, ACB, and PCB, ROIs were placed on both brain hemispheres, a total of 12 ROIs was obtained for every subject in the study (Fig. 1). The size of the ROIs varied from 15 to 25 pixels (48–80 mm^2) depending on the studied anatomical region. Special care was taken in the placement of ROIs to reduce the contamination of white matter DTI measures with gray matter due to partial volume effects present on the measured data as well as to avoid artifacts. ROIs were placed into the anatomical structures using the color-coded maps as guidance and later on used to read FA and MD values from the respective index maps with ImageJ software.

Statistical analyses

All statistical analyses have been performed using SPSS14 software (SPSS, Chicago, Illinois). For group comparisons, we computed non-parametric Mann–Whitney *U* tests. Both brain hemispheres were treated as independent variables. Non-parametric ANOVA was done to test for interaction effects (gender diagnosis). For bivariate correlations, we used the Spearman's rank correlation test, a non-parametric measure of statistical dependence between two variables. It should be noted that we did not apply Bonferroni correction for multiple comparisons. One reason is that the DTI measures FA and MD are not completely independent. Moreover, the DTI measures in the several ROIs within the subjects are also not regarded to be entirely independent.

Results

Demographic and neuropsychological data

Gender, age, and IQ did not differ between groups (Table 1). Among patients, 43% were smokers compared with 18% smokers in the control group. As expected, we found significant group differences in ADHD semiquantitative measures WURS and BADDS (Table 1). The TOVA ADHD score was significantly ($P = 3 \times 10^{-7}$) lower in ADHD patients (-4.4 ± 5.7) than in controls (1.7 ± 2.0). RT was significantly longer, and RT variability was significantly higher in ADHD patients (Table 1). In the Stroop task, performance in the patient group was also poorer, but the differences did not achieve statistical significance. As the different tests are not independent (all tasks included a substantial attentional component), we did not apply Bonferroni correction for multiple comparisons.

Table 2 Fractional anisotropy (FA) values in patients and controls

Region-of-interest		Patients		Controls		*P*
		Mean	SD	Mean	SD	
Inferior longitudinal fasciculus	R	0.56	0.09	0.57	0.08	0.39
	L	0.56	0.08	0.61	0.06	0.003
Anterior cingulum bundle	R	0.45	0.11	0.49	0.12	0.21
	L	0.51	0.14	0.54	0.1	0.26
Posterior cingulum bundle	R	0.53	0.09	0.53	0.11	0.88
	L	0.54	0.1	0.53	0.09	0.63
Inferior frontooccipital fasciculus	R	0.58	0.08	0.59	0.05	0.61
	L	0.6	0.07	0.62	0.06	0.27
Superior longitudinal fasciculus	R	0.5	0.1	0.53	0.09	0.12
	L	0.49	0.08	0.51	0.07	0.26
Corpus callosum	genu	0.87	0.07	0.85	0.07	0.28
	splenium	0.9	0.05	0.89	0.04	0.4

R Right; *L* Left; *SD* Standard deviation; uncorrected *P*-values

As of the unequal distribution of smoking status across groups, we tested whether smoking parameters (amount of daily cigarettes, years of smoking) were correlated with neuropsychological measures. We did not find any significant ($P < 0.05$) correlation within the groups nor in the entire sample.

Group differences in fractional anisotropy and mean diffusivity

The highest FA values and lowest MD values were found in the splenium of the CC, consistent with previous findings [26] (Tables 2, 3). In ADHD patients, we found reduced FA in all examined structures except in the corpus callosum and in the left PCB (Table 2). The difference achieved statistical significance in the left ILF (mean and standard deviation of FA in patients 0.56 ± 0.08, in control subjects 0.61 ± 0.06; Mann–Whitney *U* test: $Z = -2.99$, $P = 0.003$). This difference in FA values in the left ILF also remained significant when male and female subjects were investigated separately (mean FA in male patients 0.57 ± 0.07, mean FA in male control subjects 0.61 ± 0.06; Mann–Whitney *U* test: $Z = -2.02$, $P = 0.043$; mean FA in female patients 0.55 ± 0.08, mean FA in female control subjects 0.61 ± 0.07; Mann–Whitney *U* test: $Z = -2.33$, $P = 0.02$; Table 2).

However, when diagnosis and gender were treated as factors in a non-parametric ANOVA analysis with left ILF FA values as dependent variable, we found no significant effect of gender ($F = 0.29$, $P = 0.59$) and no interaction effect ($F = 0.17$, $P = 0.68$).

In ADHD patients, we found significantly increased MD in the left IFO (mean and standard deviation of MD in patients 743 ± 70, in control subjects 701 ± 51; Mann–Whitney *U* test: $Z = -2.4$, $P = 0.016$; Table 3). This difference in MD values in the left IFO also remained significant when male subjects were investigated separately (mean MD in male patients 744 ± 76, mean MD in male control subjects 690 ± 54, Mann–Whitney *U* test: $Z = -1.99$, $P = 0.047$), while the difference was not significant within the female group (mean MD in female patients 743 ± 63, mean MD in female control subjects 711 ± 46, Mann–Whitney *U* test: $Z = -1.54$, $P = 0.12$; Table 3).

Calculating a non-parametric ANOVA with diagnosis and gender as factors and left IFO MD values as dependent variable, we found no effect of gender ($F = 0.58$, $P = 0.45$) and no interaction effect ($F = 0.52$, $P = 0.47$).

Age effects on FA and MD have been previously described in healthy adults [34]. However, in our sample, age effects on imaging parameters could largely be excluded as both groups were carefully age-matched. We did not find any significant age effect in the left ILF and in the left IFO.

As there is some evidence that smoking may affect FA values [39], we also tested whether smoking status has any effect on FA. Smokers did not differ from non-smokers in the left ILF (mean FA in $N = 22$ smokers 0.57 ± 0.06, mean FA in $N = 49$ non-smokers 0.59 ± 0.08, Mann–Whitney *U* test: $Z = -1.52$, $P = 0.13$) as well as in the left IFO (mean MD in $N = 16$ smokers 734 ± 84, mean FA in $N = 24$ non-smokers 718 ± 53, Mann–Whitney *U* test: $Z = 0.52$, $P = 0.6$).

Correlation of DTI measures and parameters of attentional performance

Based on the group comparison of DTI metrics within the ROIs, we were primarily interested in the relationship of FA and MD with attentional performance in the left ILF and in the left IFO in ADHD patients. We found a significant correlation between MD and measures of attentional performance in the left ILF in ADHD patients: MD

Table 3 Mean diffusivity (MD) values in patients and controls

Region-of-interest		Patients		Controls		*P*
		Mean	SD	Mean	SD	
Inferior longitudinal fasciculus	R	797	49	803	47	0.63
	L	793	58	805	43	0.35
Anterior cingulum bundle	R	746	83	761	71	0.42
	L	775	73	745	83	0.11
Posterior cingulum bundle	R	732	71	730	47	0.89
	L	737	64	737	51	0.98
Inferior frontooccipital fasciculus	R	753	50	758	45	0.71
	L	744	70	701	51	0.016
Superior longitudinal fasciculus	R	779	60	778	55	0.91
	L	764	75	754	68	0.53
Corpus callosum	genu	690	71	719	82	0.11
	splenium	683	91	689	79	0.79

R Right; *L* Left; *SD* Standard deviation; uncorrected *P*-values

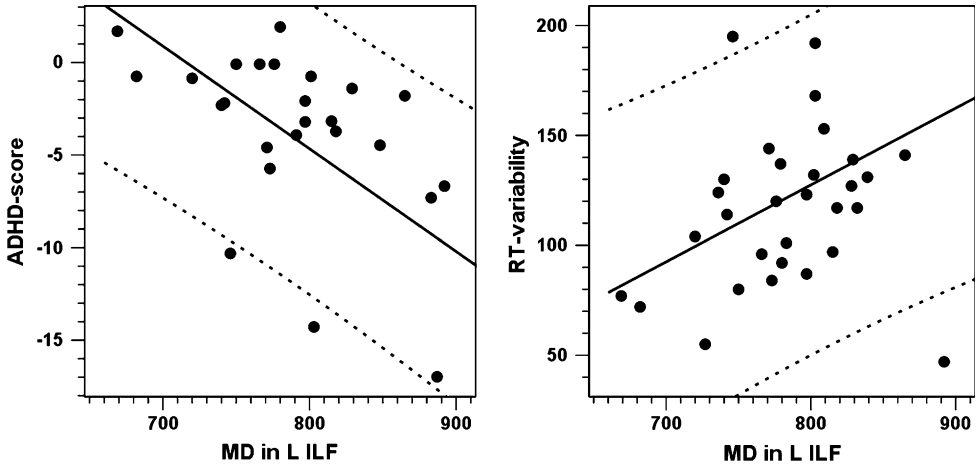

Fig. 2 Regression analysis between mean diffusivity (MD) and measures of attentional performance in the left inferior longitudinal fasciculus (ILF) in ADHD patients. *Left* regression between MD and ADHD score (TOVA; Spearman's correlation coefficient $r = -0.63$, $P = 5.4 \times 10^{-4}$). *Right* regression between MD and RT-variability ($r = 0.42$, $P = 0.016$)

was negatively correlated with the ADHD score (TOVA; Spearman's correlation coefficient $r = -0.63$, $P = 5.4 \times 10^{-4}$) and with RT-variability ($r = 0.42$, $P = 0.016$; Fig. 2). In ADHD patients, the other correlations of FA/MD in the ROIs and attentional parameters were not significant or just missed significance. Also, no significant correlation between DTI measures and attentional performance was seen within the group of healthy controls.

Discussion

The main finding of this study was that left frontotemporal white matter changes in adult ADHD patients were seen compared with healthy control subjects. In particular, we found lower FA in the left ILF and higher MD in the left IFO in ADHD patients, and these differences were found in both female and male patients (except MD in the left IFO in women). We were therefore in part able to confirm the results of the voxel-based analysis of the same MR-DTI data set in which we demonstrated reduced FA as well as higher MD bilaterally in orbitomedial prefrontal WM [31]. This previous work and its limitations have been commented by Castellanos and Hyde, emphasizing that the results have to be interpreted with caution as they would not have survived correction for multiple comparisons [13].

Besides our previous work [31], the only other published MR-DTI investigation in adult ADHD patients by Makris et al. [36] found lower FA values in the right cingulum bundle and the right SLF using ROIs which included only the cingulum bundle and the SLF. The authors hypothesized that fiber tracts subserving attention and executive functions would be altered in ADHD patients and therefore investigated only a small number of ROIs (cingulum bundle, SLF) in their study, which did not include temporal and frontal WM structures [36]. Casey et al. [11] performed a multimodal fMRI and MR-DTI study and demonstrated that FA in right prefrontal fiber tracts correlated with functional activity in the inferior frontal gyrus and caudate nucleus. In ADHD children and adolescents,

Ashtari et al. [1] performed a voxel-based MR-DTI analysis and identified clusters of significantly decreased FA in several brain areas (right premotor cortex, right anterior limb of the internal capsule, right cerebral peduncle, middle cerebellar peduncle, left cerebellum, and left parieto occipital region). In the context with our finding in the temporal lobe, it is of particular interest that a recent functional MRI study demonstrated temporal lobe dysfunction in boys with ADHD [44]. Another multimodal imaging study in ADHD children pointed to the right temporal gyrus as highly affected locus in ADHD [30].

The sample heterogeneity between studies is a possible reason for these discrepant findings. Another reason could be the medication status of the investigated patients. In contrast to the majority of imaging studies in ADHD including the previously conducted MR-DTI studies, we only included never-medicated patients in our study. In particular, none of the patients had received any ADHD-specific treatment before. Any potential medication effects on our imaging results as well as on neuropsychological findings could therefore be excluded. This is potentially meaningful because it has been demonstrated that stimulant medication leads to increased activation in frontostriatal and cerebellar regions [17, 54]. Of course, the discrepant findings between studies could also be the result of different diffusion imaging parameters between studies. For instance, at the time of the initiation of the study in 2003, it was still standard to acquire DTI data sets in six non-collinear diffusion-sensitizing gradient directions. Despite the limitations of the six-direction procedure, we were able to detect statistically significant group differences in DTI metrics in the left IFO and in the left ILF, while the methodology might have produced false-negative findings in other ROIs. The long duration of our investigation was mostly due to the inclusion of highly selected patients. In particular, we exclusively enrolled unmedicated patients, and we made every effort to achieve certainty about the ADHD diagnosis. In addition to clinical interviews which included follow-up investigations, we used a large neuropsychological test battery in order to exclude ADHD patients with psychiatric comorbidity. As our study is limited to combined-type ADHD patients, our findings cannot be assigned to the inattentive or hyperactive subtype.

Interestingly, we found a significant correlation of MD with measures for attentional performance (TOVA ADHD score, RT variability) in the left ILF in ADHD patients (Fig. 2). This is in line with the notion that the occipito-temporal tract (ILF) is part of the sensory visual attentional network, while the ACB is particularly involved in directed attentional and executive functions. In general, this observation also supports the notion that the observed difference in FA values between ADHD patients and controls in the left ILF is clinically relevant and not merely an epiphenomenon. In this context, it is also noteworthy that the correlation between MD values and attentional performance was not seen in healthy control subjects. This could indicate that lower FA values in ADHD patients are the result of an ADHD-specific pathological process rather than the extreme end of a continuum in the general population. Though, a MR-DTI study investigating women with borderline personality disorder and comorbid ADHD did not find any association between test performance and MR-DTI parameters [45]. We were not able to confirm the results of our previous voxel-based analysis showing a correlation between attentional performance and DTI measures in parts of the SLF [31]. Though, in our ROI analysis, we investigated only a small portion of the posterior SLF, which may explain the lack of significant correlation. It has to be mentioned that the results of our correlation analyses can only be explorative, and a meaningful interpretation of the data is difficult.

The question of what pathological process may underlie the abnormality of FA and MD values in ADHD patients currently cannot be answered. FA and MD have been described as parameters for white matter integrity, but its biological determinants are not yet entirely clarified [32, 38, 46]. Myelin sheaths and axonal membranes represent the main barriers for water diffusion in white matter tissue, and the number of fiber crossings within white matter regions also influences water diffusion. In addition, the number or density of axon fibers and the coherence of these fibers influence DTI parameters as well [38]. For instance, higher FA in WM tracts is associated with higher density of fibers or larger diameter of fibers [5]. In this context, it is of particular interest to discuss the contrary findings of the current ROI analysis and our previous voxel-based analysis in temporal white matter tracts: In the ROI analysis of the left ILF, we found significantly decreased FA, which may correlate with reduced integrity of this large association tract. The significant clusters in our previous analysis with significantly higher FA in the ADHD patient group were located more superior bilaterally in temporal WM, including predominantly portions of the IFO and the uncinate fasciculus [31]. As mentioned by us previously [31] and discussed by Castellanos and Hyde [13], these results may be due to the particular high amount of fiber crossings in this region, and higher FA in ADHD subjects may be associated with a fewer fiber crossings but not with higher white matter integrity. Taken together, it is difficult to tell what biological processes exactly account for the observed FA and MD differences between ADHD patients and healthy control subjects in our study.

In this context, it is also important to mention that a number of electroencephalography (EEG) studies demonstrated impaired functional connectivity, i.e., coherence, in ADHD, particularly in frontal areas, though most of these

studies have been conducted in children: ADHD children showed contrasting coherence effects in the lower (ADHD elevated) and upper (ADHD reduced) alpha range, suggesting a deficient resting-state connectivity in ADHD and a stimulus-induced state of over-connectivity within and between frontal hemispheres [37]. Reduced interhemispheric alpha and delta coherence as a measure of functional connectivity has been shown in adult ADHD [15]. Moreover, a recent simultaneous EEG/fMRI study with a go/no-go task investigating response inhibition and voluntary selection demonstrated reduced brain responses in frontal areas in adult ADHD patients [29].

Taken together and in light of previous neuroimaging studies, our finding of frontobasal and left temporal WM changes in adult ADHD patients supports the notion that structural brain abnormalities may not be restricted to the frontal–striatal–cerebellar circuitry as suggested by previous studies. In fact, our results rather point to an involvement of left temporal WM structures, and these structural abnormalities are correlated with measures for attentional performance.

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Conflict of interest None.

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