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COGNITIVE NEUROSCIENCE

Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder

EJN FEATURED ARTICLE

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Abstract

Inattention and impulsivity are the most prominent clinical features of attention deficit hyperactivity disorder (ADHD) in adulthood. Structural and functional neuroimaging studies of subjects with ADHD have demonstrated abnormalities in several brain areas, including fronto-striatal and fronto-cerebellar networks. Mostly, these studies were based on volumetric measurements and have been conducted in children. We investigated white matter (WM) integrity and correlation with measures of attention and impulsivity in adult patients with ADHD adopting diffusion tensor imaging (DTI). $N = 37$ (21 males) never-medicated adult patients with ADHD combined subtype and $N = 34$ (16 males) healthy controls were investigated. ADHD diagnosis (DSM-IV) was assessed with clinical interviews and rating scales, subjects also underwent a large neuropsychological test battery including tests of attention and impulsivity. DTI was acquired, and group differences of fractional anisotropy (FA) and mean diffusivity (MD) as well as correlation analyses with measures of attentional performance and impulsivity were calculated using voxel-based analyses. In adult patients with ADHD, 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. 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 fibre tracts. This is the first DTI study demonstrating disturbed structural connectivity of the frontal-striatal circuitry in adult patients with ADHD. Moreover, a direct correlation between WM integrity and measures of attention and impulsivity is shown.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a frequent psychiatric disorder in childhood and adolescence persisting into adulthood in a considerable number of patients (Faraone *et al.*, 2000). Inattention and impulsivity are the most prominent clinical features of ADHD in adulthood (Seidman *et al.*, 2004). ADHD is highly heritable, and there is convergent evidence that it may be associated with neurobiological deficits in the fronto-striatal network (Castellanos, 1997; Spencer *et al.*, 2002; Emond *et al.*, 2009).

Neuroimaging studies of subjects with ADHD have been predominantly conducted in children and adolescents, and have been mostly based on magnetic resonance imaging (MRI) measurements (for review, see: Seidman *et al.*, 2005; Valera *et al.*, 2007). Volumetric MRI studies primarily demonstrated abnormalities of the fronto-striatal circuitry [e.g. dorsolateral prefrontal cortex, basal ganglia, anterior cingulate cortex (ACC)], but there is also growing literature supporting fronto-cerebellar abnormalities in ADHD (Castellanos, 1997; Giedd *et al.*, 2001; Seidman *et al.*, 2005; Valera *et al.*, 2007). To date, only few MRI studies in adult patients with ADHD have been published (Hesslinger *et al.*, 2002; Seidman *et al.*, 2006; Makris *et al.*, 2007, 2008). Smaller overall cortical grey matter, prefrontal and ACC volumes in adult patients with ADHD have been shown (Seidman *et al.*, 2006), emphasizing that these areas are involved in attention and executive control. Moreover, a significant reduction of the volume of the left orbitofrontal cortex in adult patients with ADHD has been demonstrated (Hesslinger *et al.*, 2002).

During the last years, diffusion tensor imaging (DTI) became available to investigate human brain microstructure, i.e. the integrity of white matter (WM) fibre tracts. With DTI, diffusion of water molecules can be characterized by two diffusion parameters: (i) mean diffusivity (MD), which measures the rotationally invariant magnitude of water diffusion; and (ii) fractional anisotropy (FA), which provides an index of directional selectivity of water diffusion (Beaulieu, 2002). In brain WM, myelination properties, fibre organization, axonal

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diameter, fibre density and the ratio of intracellular/extracellular space contribute to differences in FA and MD (Beaulieu, 2002; Schmithorst *et al.*, 2002). Using DTI, microstructural properties of brain regions in ADHD have been investigated only by a few groups: based on a voxel-based DTI analysis, decreased FA has been demonstrated predominantly in the frontal and cerebellar WM in children with ADHD (Ashtari *et al.*, 2005). Another study showed decreased FA in the superior longitudinal fasciculus (SLF) and in the corticospinal tract in children and adolescents with ADHD using a tract-based atlasing approach on DTI data (Hamilton *et al.*, 2008). Recently, Pavuluri *et al.* (2009) reported reduced FA in the anterior corona radiata in children and adolescents with ADHD. Makris *et al.* (2008) 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 patients with ADHD. A multimodal MRI study reported a correlation of FA in prefrontal fibre tracts and a measure of impulsivity (performance in a go/no-go task) in parent–child diads with ADHD (Casey *et al.*, 2007), though the correlation between DTI measures and neuropsychological measures of attention has not yet been investigated.

Finally, most functional imaging studies in ADHD demonstrated abnormal activation primarily in frontal cortices and the anterior cingulum (Schulz *et al.*, 2004, 2005; Bush *et al.*, 2005; Durston *et al.*, 2006). This is largely in line with structural imaging studies showing abnormalities particularly in these cortical regions and adjacent WM structures. However, these functional studies have also mostly been conducted in children and adolescents.

The aim of the present DTI study was to examine structural connectivity in a large sample of never-medicated, adult patients with ADHD compared with healthy control subjects. In addition to previous DTI studies in adult ADHD, we investigated whether microstructural integrity is directly correlated with attentional performance and impulsivity. We hypothesized that frontostriatal connectivity may particularly be involved in ADHD pathophysiology, and that disturbed frontostriatal connectivity may correlate with clinical measures of inattention and impulsivity.

Materials and methods

Subjects

We investigated 37 adult patients with ADHD (21 males; mean age 32.5 years, range 18–49 years) and 34 healthy control subjects (16 males; mean age 30.2 years, range 19–53 years; Table 1). All patients were recruited from the outpatient clinic of the Department of Psychiatry and Psychotherapy of the University Medical Centre Mainz (Germany). Control subjects were recruited via local newspaper announcements. All subjects were right-handed Caucasians. Patients and control subjects were enrolled during a relatively long period of approximately 4 years, primarily due to the careful selection of patients with ADHD.

We included only patients with the combined ADHD type, diagnosis was assessed as described below. Moreover, in patients with ADHD, additional acute psychiatric disorders were excluded by clinical interviews over a period of 6 months before and a 6 months 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) < 80.

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. Moreover, control subjects did not have any current or past psychotropic medication. Written informed consent was obtained from all study participants. The study was approved by the Ethics Committee of the Johannes Gutenberg-University in Mainz (Germany) and in accordance with the Declaration of Helsinki.

TABLE 1. Sociodemographic and neuropsychological data

	ADHD patients	Controls	*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}*
Commission errors (TOVA)	9.5 ± 7.0	4.6 ± 3.7	0.001*
TMT-A	30.2 ± 9.7	24.3 ± 10.1	0.02*
TMT-B	70.9 ± 27.0	54.8 ± 22.0	0.009*
MWT-B	27.4 ± 3.9	28.9 ± 4.4	0.13
AVLT	54.9 ± 9.9	63.0 ± 7.6	0.001*
WMS-R	132.6 ± 16.7	144.9 ± 21.7	0.02*
WCST (number of errors)	35.2 ± 18.6	25.3 ± 28.0	0.14
WURS	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}*

ADHD, attention deficit hyperactivity disorder; AVLT, Auditory-Verbal Learning Test; BADDS, Brown Attention-Deficit Disorder Scale for Adults; IQ, intelligence quotient; MWT-B, Multiple Choice Vocabulary Test; RT, reaction time; TMT, Trail Making Test; TOVA, Test of Variables of Attention; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale-Revised; WURS, Wender Utah Rating Scale. Data are presented as means ± SD. **P* < 0.05.

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 (Krause & Krause, 2002). 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 seven subcategories (Rosler *et al.*, 2008). The German short version (Retz-Junginger *et al.*, 2002) of the Wender Utah Rating Scale (WURS-k) is considered to be a sensitive aid in the retrospective diagnosis of childhood ADHD (Ward *et al.*, 1993). In addition, we acquired information from parents and school certificates from primary school. A retrospective childhood diagnosis of ADHD was established in all patients using a cutoff value of 30 points in the WURS-k, with five patients having already a pre-existing diagnosis of childhood ADHD. We tested present symptomatology using the Brown Attention-Deficit Disorder Scale for Adults (BADDS; Brown, 1996).

To examine for psychiatric comorbidity, we performed the German versions of the structured clinical interview for DSM-IV (SCID-I and SCID-II; Fydrich *et al.*, 1997; Wittchen *et al.*, 1997), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman *et al.*, 1989), the Beck Depression Inventar (BDI; Beck & Steer, 1987), and the Social Phobia and Anxiety Inventory (SPAI; Beidel *et al.*, 1989). Smoking status was assessed by the number of cigarettes per day and years of smoking.

All patients and control subjects underwent a large neuropsychological test battery: the ADHD score as a measure of attentional performance was assessed with the Test of Variables of Attention (TOVA; Greenberg & Kindschi, 1996), which was also used to measure mean reaction time (RT) and RT variability. Moreover, the number of commission errors was assessed in the TOVA as a measure for impulsivity (Aggarwal & Lillystone, 2000). IQ was measured by the Achievement Measure System (*Leistungspruefsystem*, LPS; Horn, 1983), which is a common standardized German test to measure general intelligence. We adopted a short form of the LPS, which consists of six subtests (general intelligence, reasoning, word fluency, spatial imagination, figure-ground segregation, and recognition of words; Sturm & Willmes, 1983). Results of LPS are given in terms of IQ scores with a mean of 100 and a standard deviation of 15. The multiple choice vocabulary test (*Mehrfachwahl Wortschatztest-Form* B, MWT-B) is a German test to measure verbal intelligence and is thought to be a valid indicator of pre-morbid intelligence (Lehrl, 1989). Memory functions were tested by the Auditory-Verbal Learning Test (AVLT; Schmidt, 1996) and the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987). The Trail Making Test (TMT; Reitan, 1992) was assessed to measure visuospatial ability (TMT-A) and executive function (TMT-B). The Wisconsin Card Sorting Test (WCST) was also conducted to test executive function (Heaton *et al.*, 1993).

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 (Fellgiebel *et al.*, 2004). DTI images were acquired with a transversal diffusion-weighted single-shot spin-echo echo-planar-based sequence in six non-collinear diffusion-sensitizing gradient directions with diffusion sensitivity $b = 900\ \text{mm}^2/\text{s}$ and one acquisition without diffusion encoding ($b = 0\ \text{mm}^2/\text{s}$). The acquisition matrix was 128×128, with 5 mm slice thickness. Repetition time (TR) was 8000 ms, echo time (TE) was 100 ms. All transversal slices were arranged parallel to the AC–PC line. At the time when the study was planned in 2003, these were standard imaging parameters.

Image pre-processing and voxel-based analysis of DTI data

Original MR diffusion images were registered in DICOM format and converted to ANALYZE format using MRICRO software (University of Nottingham, UK). All scans were inspected visually. None of the data sets in our sample had to be excluded. The T2-weighted images were normalized to the MNI (Montreal Neurological Institute) T2 template using SPM2 (statistical parametric mapping; Wellcome Department of Cognitive Neurology, London, UK) software implemented in MatLab 6.5 (Mathworks, Sherborn, MA, USA). Identical normalization parameters were used for warping of the diffusion-weighted images such that each voxel represents the same part of the brain in every subject. For the calculation of FA and MD maps, the FDT tool (FMRIB's Diffusion Toolbox) of the FSL software library (FMRIB's software library) was used. The obtained FA and MD maps were then smoothed with a 9-mm isotropic FWHM Gaussian kernel to improve signal-to-noise ratio and normalization.

Voxel-based FA and MD contrast analyses were then done to compare ADHD patient and control groups using General Linear Model (GLM) standard independent sample *t*-test. In addition, voxel-based regression analyses were performed with two contrasts to investigate whether each voxel had a significant positive or negative correlation of FA and MD with the following measures of clinical symptomatology: the ADHD score from the TOVA as a measure for attentional performance; the number of commission errors in the TOVA as a measure of impulsivity; and the BADDS as a measure for present total ADHD symptomatology.

The contrast maps for group and regression analyses were thresholded at $P < 0.001$ without correction for multiple comparisons, and the extent threshold for significant clusters was set to 40 voxels. We were aware that the application of an uncorrected threshold would certainly limit the impact of possible results as it increases the probability of false positive findings. To justify the selection of an uncorrected threshold in our analyses, we provide the following issues. Taking into account the results of previous findings in DTI studies in ADHD (Ashtari *et al.*, 2005; Makris *et al.*, 2008), we only expected discrete microstructural abnormalities in ADHD that may not be detectable adopting a corrected threshold with a much higher risk of false negative findings. In this context, it is noteworthy that the only published voxel-based DTI study in ADHD – like a large number of imaging studies in the neuropsychiatric field – also used an uncorrected ($P < 0.001$) threshold (Ashtari *et al.*, 2005).

T1-weighted templates were then overlaid with the statistically significant SPM clusters using MRICRO software for graphical presentation in neurological convention. The MRI atlas of human WM (Mori *et al.*, 2005) was used for the identification of subcortical WM structures. The MNI coordinates and *t*-statistic of the peak voxel, the cluster size and the corresponding anatomical structures were determined (Mori *et al.*, 2005).

Regression analysis of peak voxel DTI measures and measures of ADHD symptomatology

The mean FA and MD values of the peak voxel resulting from the voxel-based group analysis as well as from the voxel-based regression analyses were correlated with the measures for attentional performance (ADHD score), impulsivity (number of commission errors) and total ADHD symptomatology (BADDS score). Significance was set to $P < 0.05$ (uncorrected) for these regression analyses.

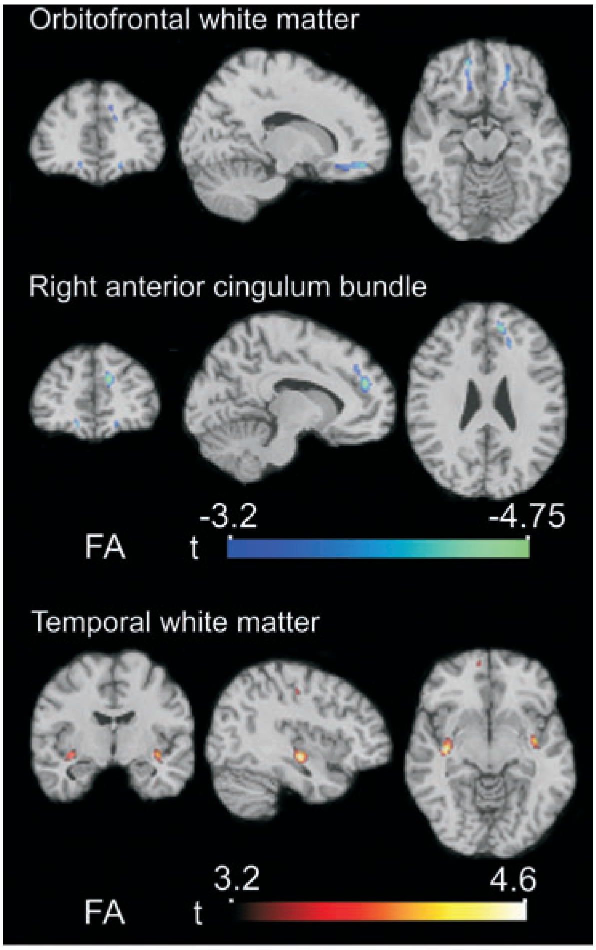
Results

Demographic and neuropsychological data

Gender, age and IQ did not differ between groups (Table 1). Among patients, 16 (43%) were regular smokers, compared with 6 (18%) regular smokers in the control group. As expected, we found significant group differences in ADHD semi-quantitative measures WURS and BADDS (Table 1). The ADHD score (TOVA) was significantly lower in patients with ADHD (-4.4 ± 5.7) than in controls (1.7 ± 2.0). RT was significantly longer and RT variability was significantly higher in patients with ADHD (Table 1). Patients' performance was significantly poorer in the TMT-A, in the TMT-B, in the AVLT and in the WMS-R (Table 1). In the remaining neuropsychological tests (MWT, WCST), performance in the patient group was also poorer, but the differences did not achieve statistical significance (Table 1). As the tests examined different categories of neuropsychological performance and executive function, we did not use a Bonferroni correction for multiple comparisons.

Group differences in FA

Voxel-wise parametric FA contrast analyses between patients and controls revealed statistically significant group differences (thresholded at an uncorrected $P < 0.001$ on voxel-level) in the following brain areas (Fig. 1; Table 2): FA was found to be significantly lower in the ADHD patient group in the right anterior cingulum bundle (ACB) as well as bilaterally in orbitofrontal WM structures. These orbitofrontal areas include primarily frontal parts of the inferior frontooccipital fasciculus (IFO), parts of the anterior thalamic radiation and portions



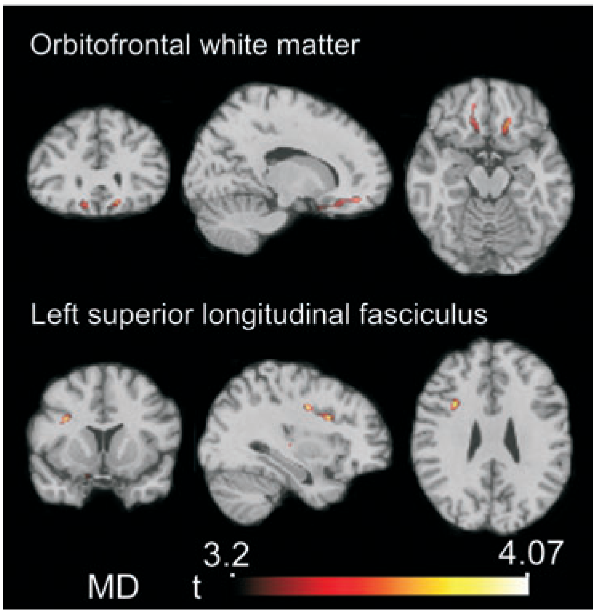


FIG. 1. Group differences in fractional anisotropy (FA) and mean diffusivity (MD) between $N = 37$ patients with ADHD and $N = 34$ control subjects. Significant decreased FA in patients with ADHD bilaterally in orbitofrontal WM and in the right ACB. Significant increased FA in patients bilaterally in the temporal WM. Significant increased MD in patients with ADHD bilaterally in orbitofrontal WM and in the left SLF. Represented results are thresholded at a $P < 0.001$ (uncorrected) and overlaid on T1 templates in neurological convention (R = R).

of the corpus callosum (CC). Clusters with significantly higher FA in the patient group were found bilaterally in the temporal WM, including predominantly portions of the IFO and the uncinate fasciculus (Figs 1 and 2; Table 2).

Because of the unequal distribution of smoking status across groups (Table 1) and because there is some evidence that smoking may affect DTI measures (Paul *et al.*, 2008), we performed an additional analysis with smoker status as covariate: the results for the group differences were essentially identical to those described above.

Group differences in MD

Voxel-wise parametric MD contrast analyses between the groups demonstrated statistically significant group differences ($P < 0.001$, uncorrected) in the left SLF as well as bilaterally in frontoorbital WM structures including the IFO and the uncinate fasciculus, extending into the anterior thalamic radiation. In the ADHD patient group, MD was found to be significantly higher in these areas (Figs 1 and 2; Table 2). The results of the additional analysis with smoker status as covariate were essentially identical.

Correlation of DTI parameters and measures of attention, impulsivity and total ADHD symptomatology

Within the ADHD patient group, we performed correlation analyses of FA and MD with the ADHD score of the TOVA as a measure of attentional performance. We found significant ($P < 0.001$, uncorrected) positive correlation between FA and the ADHD score, as well as significant negative correlation between MD and the ADHD score in the right SLF (Fig. 3; Table 3). Correlation analyses of FA and MD with the number of commission errors in the TOVA as a measure of impulsivity revealed significant ($P < 0.001$, uncorrected) negative correlation between FA and the number of commission errors in right frontobasal WM, including parts of the right fasciculus uncinatus and the right anterior thalamic radiation. Significant positive correlation between MD and the number of commission errors was present bilaterally in the lingual gyrus (Fig. 3; Table 3). We did not find any significant correlations of DTI parameters and BADDS within the patient group.

Within the control group, the voxel-based correlation analyses of FA and ADHD score revealed a significant cluster of positive correlation in the right SLF (peak voxel MNI 22, −36, 40; $t = 4.19$; 101 voxels). The correlation analysis of FA and ADHD score, as well as the correlation analyses of MD and ADHD score and impulsivity (number of commission errors) did not provide any significant results ($P < 0.001$, uncorrected).

On the other hand, we did not find any significant ($P < 0.05$) correlations of attentional performance and impulsivity (ADHD score and number of commission errors in the TOVA) with FA or MD in the peak voxels. This may indicate that the most affected brain regions in our sample of patients with ADHD do not necessarily account for most of the variance with regard to inattention and impulsivity.

Discussion

Abnormalities of WM integrity in adult ADHD

One novel finding of this study is that bilateral orbitofrontal WM changes in adult patients with ADHD were seen compared with matched healthy control subjects (Fig. 1). These areas include fronto-striatal fibre tracts connecting prefrontal cortices with putamen and caudate nucleus. The uncinate fasciculus connects orbitofrontal and

TABLE 2. Group differences in FA and MD between $N = 37$ patients with ADHD and $N = 34$ control subjects

Brain area	DTI measure	Contrast	Peak voxel MNI	Peak voxel *t*-value	Cluster size (voxels)
R anterior cingulum bundle	FA	ADHD < controls	10, 46, 18	4.75	110
L orbitofrontal WM	FA	ADHD < controls	−16, 50, −20	4.36	89
R orbitofrontal WM	FA	ADHD < controls	16, 38, −22	4.2	64
L temporal WM	FA	ADHD > controls	−38, −14, −8	−4.6	153
R temporal WM	FA	ADHD > controls	36, −6, −6	−4.38	87
L superior longitudinal fasciculus	MD	ADHD > controls	−34, −4, 24	−3.86	41
L orbitofrontal WM	MD	ADHD > controls	−14, 26, −30	−3.76	145
R orbitofrontal WM	MD	ADHD > controls	14, 30, −28	−3.98	68

ADHD, attention deficit hyperactivity disorder; DTI, diffusion tensor imaging; FA, fractional anisotropy; L, left; MD, mean diffusivity; MNI, Montreal Neurological Institute; R, right; WM, white matter. Given are significant ($P < 0.001$, uncorrected) clusters.

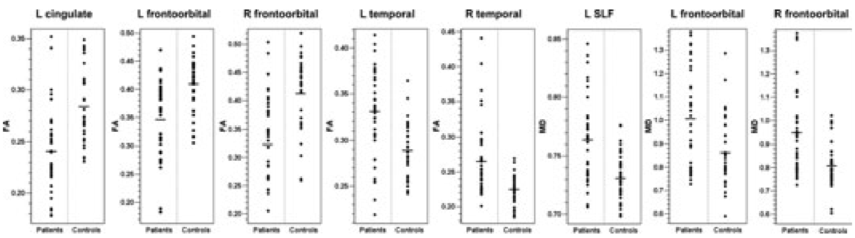


FIG. 2. Scatterplots for group comparisons between patients with ADHD and control subjects. Presented are fractional anisotropy (FA) and mean diffusivity (MD) values in the peak voxels of the voxel-based analysis. L, left; R, right; SLF, superior longitudinal fasciculus.

subcortical limbic regions, which have been shown to modulate emotional behaviour and stress responses (Drevets, 2000; Beyer *et al.*, 2005). Disturbed WM microstructure of the limbic-thalamic-cortical circuits has already been demonstrated in mood disorders (Drevets, 2000; Versace *et al.*, 2008). Several MRI studies in patients with ADHD showed volume reductions in prefrontal cortices (Seidman *et al.*, 2005; Valera *et al.*, 2007) and in the orbitofrontal cortex (Hesslinger *et al.*, 2002). Makris *et al.* (2007) found significant cortical thinning in ADHD in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal and the ACCs. Casey *et al.* (2007) performed a multimodal functional MRI and DTI study, and demonstrated that FA in right prefrontal fibre tracts was correlated with functional activity in the inferior frontal gyrus and caudate nucleus, though they did not describe FA differences between patients with ADHD and controls. A DTI study in women with borderline personality disorder (BPD) and comorbid ADHD investigated inferior frontal WM, but did not find differences between patients and healthy control subjects (Rusch *et al.*, 2007). In addition, there is also convergent evidence from neuropsychological, genetics and neurochemical studies pointing to the involvement of the fronto-striatal network in the pathophysiology of ADHD (for review, see: Emond *et al.*, 2009).

Our results of reduced FA in the right ACB are in line with previous findings in adult patients with ADHD showing reduced FA in the ACB and SLF in the right hemisphere (Makris *et al.*, 2008). The ACB is part of the attentional network and involved in cognitive processing (Mesulam, 1990; Baird *et al.*, 2006; Mulert *et al.*, 2008). Moreover, several volumetric MRI studies in adult patients with ADHD showed reduced regional brain volume predominantly in the ACC, prefrontal cortex, cerebellum, caudate and CC (Seidman *et al.*, 2006; Valera *et al.*, 2007). Though there is a discrepancy between our results and the DTI studies in children and adolescents with ADHD. Ashtari *et al.* (2005) performed a voxel-based DTI analysis in children and adolescents with ADHD and showed significantly decreased FA in the right premotor cortex, right anterior limb of the internal capsule, right cerebral peduncle, middle cerebellar peduncle, left cerebellum and left parietooccipital region. Another recent DTI study in children and adolescents with ADHD investigated eight fibre tracts including the cingulum, inferior longitudinal fasciculus and SLF (Pavuluri *et al.*, 2009): MD was significantly higher in patients with ADHD in these regions, but no difference was observed for FA values (Pavuluri *et al.*, 2009). Moreover, decreased FA in the SLF and in the corticospinal tract in children and adolescents with ADHD has been demonstrated (Hamilton *et al.*, 2008).

Our findings of increased FA bilaterally in frontotemporal WM connections point to an involvement of widespread brain areas in the pathophysiology of ADHD. While temporal structural abnormalities have not yet been described in previous MRI and DTI studies, a recent functional MRI study demonstrated bilateral temporal lobe dysfunction in boys with ADHD (Rubia *et al.*, 2007).

Possible reasons for the discrepancy with respect to the results of DTI studies in childhood and adolescence could be the sample heterogeneity between studies, the medication status of the investigated patients and the different diffusion imaging parameters between studies. In contrast to the majority of imaging studies in ADHD, we only included never-medicated patients in our study. Particularly, none of the patients had received any ADHD-specific treatment before such as psychostimulant medication. We are therefore able to exclude potential medication effects on imaging results as well as on neuropsychological findings. In addition, we have excluded patients with ADHD with acute psychiatric comorbidity. Although we did not include medicated patients and patients with acute psychiatric comorbidity, symptom severeness of our patients as measured with the BADDS was quite high (Brown, 1996; Table 1).

For completeness, it also needs to be mentioned that the possibility of false positive results in our study cannot be entirely excluded. In fact, taking into account the relatively weak group differences in our study, which would not survive a correction for multiple comparisons, and also the findings in DTI studies conducted by other groups in (adult) ADHD (Casey *et al.*, 2007; Makris *et al.*, 2008), replication studies would be desirable to confirm these findings.

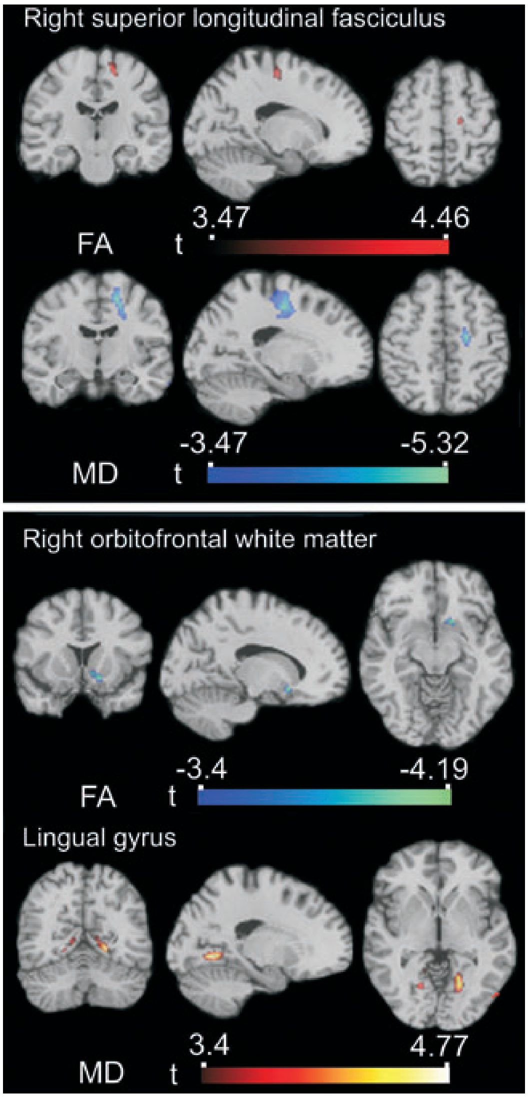


FIG. 3. Correlation between fractional anisotropy (FA) and mean diffusivity (MD) with measures of attention and impulsivity in patients with ADHD. Significant positive correlation between FA and the ADHD score, and significant negative correlation between MD and the ADHD score in $N = 26$ patients with ADHD in the right SLF (top rows). Significant negative correlation between FA and the measure of impulsivity from the TOVA in right orbitofrontal WM, and significant positive correlation between MD and the measure of impulsivity from the TOVA bilaterally in the lingual gyrus in $N = 31$ patients with ADHD (lower rows). Represented results are thresholded at $P < 0.001$ (uncorrected) and overlaid on T1 templates in neurological convention (R = R).

Correlation of diffusion parameters with attentional performance

To our knowledge, this is the first study demonstrating a direct association between microstructural integrity and measures of attention in adult patients with ADHD. The correlation analyses between diffusion parameters and the ADHD score, which reflects the ability to focus attention (Greenberg & Kindschi, 1996), demonstrated significant findings in the right SLF. This specific fibre pathway together with the cingulum bundle connects frontal areas and cortical regions at the right temporo-occipito-parietal junction, which are considered to play a key role in processing information related to attentional functions (Makris *et al.*, 2008). Even if there is a lack of structural MRI studies investigating correlations of brain (micro-) structure and attentional performance, there are convergent data from functional MRI studies adopting tasks of attention: among the most reported findings is reduced activation in the dorsal ACC, the frontal cortex and the basal ganglia, but also in right hemispheric temporal and parietal brain regions (Emond *et al.*, 2009; Rubia *et al.*, 2009). Moreover, cortical thinning in patients with ADHD compared with matched controls has been demonstrated in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal and the ACCs (Makris *et al.*, 2007).

Taken together, our finding of significant correlation between ADHD score and diffusion parameters in the right SLF suggests that structural dysconnectivity may – at least in part – underlie the described functional deficits in cortical areas connected by the right SLF.

Correlation of diffusion parameters with impulsivity

In our study, we demonstrated a significant correlation of FA and a measure of impulsivity (number of commission errors) in right fronto-striatal fibre tracts connecting the orbitofrontal cortex to the basal ganglia and limbic regions. We were therefore able to confirm in part the findings by Casey *et al.* (2007), who demonstrated a correlation of FA bilaterally in prefrontal fibre tracts and a measure of impulsivity (performance in a go/no-go task) in parent–child diads with ADHD. Impulsivity due to impaired inhibitory control functions of the fronto-striatal circuit have been described previously (Jentsch & Taylor, 1999; Uhlikova *et al.*, 2007). In this context, it is also noteworthy that a DTI study in women with BPD and comorbid ADHD demonstrated a correlation of MD in inferior frontal WM with dysfunctional affect regulation and other clinical symptoms of BPD (Rusch *et al.*, 2007). A MRI study adopting a fibre-tracking algorithm demonstrated that fronto-striatal microstructural properties predicted RT, and this correlation grew stronger for trials expected to require greater control (Liston *et al.*, 2006). The authors suggest that fronto-striatal connectivity may contribute to developmental and individual differences in

TABLE 3. Correlation of DTI measures with measures of attention and impulsivity

Brain area	Behavioural measure	DTI measure	Peak voxel MNI	Peak voxel *t*-value	Cluster size (voxels)
R superior longitudinal fasciculus	Attention (ADHD score)	FA	14, −18, 62	4.46	72
R superior longitudinal fasciculus		MD	20, −12, 48	−5.32	526
R fasciculus uncinatus/R anterior thalamic radiation	Impulsivity (commission errors in TOVA)	FA	14, 14, −16	−4.19	46
L lingual gyrus		MD	−12, 58, −2	4.02	128
R lingual gyrus		MD	20, −64, −10	4.77	171

ADHD, attention deficit hyperactivity disorder; DTI, diffusion tensor imaging; FA, fractional anisotropy; L, left; MD, mean diffusivity; MNI, Montreal Neurological Institute; R, right; TOVA, Test of Variables of Attention. Given are significant ($P < 0.001$, uncorrected) clusters.

the efficient recruitment of cognitive control (Liston *et al.*, 2006). This is of particular interest as there is a strong relation between cognitive control and impulsivity, and a lack of cognitive control has been described as an underlying deficit in ADHD that affects cognitive functioning and behaviour (Randall *et al.*, 2009). Deficiencies in the control of cognitive resources may be causal for ADHD symptoms such as inattention and impulsivity rather than impaired cognitive resources *per se* (Doyle *et al.*, 2005).

We were able to show a positive correlation of MD and impulsivity bilaterally in the lingual gyrus, which is difficult to interpret. The lingual gyrus is connected to the limbic system by neural pathways, but there are no direct connections to the fronto-striatal system, although there is some evidence from literature for correlations of DTI measures of the lingual gyrus and impulsivity in schizophrenia (Hoptman *et al.*, 2004). Taken together, our findings particularly emphasize the impact of structural integrity of fronto-striatal fibre tracts on impulsivity in adult patients with ADHD.

Neuroanatomical correlates of DTI measures

It is difficult to tell what biological processes exactly account for the observed abnormality of FA and MD values in patients with ADHD as the neuroanatomical and physiological correlates of diffusion parameters are not yet entirely understood (Beaulieu, 2002; Versace *et al.*, 2008). In our study, lower FA and higher MD in orbitofrontal areas of patients with ADHD may correlate with myelination deficits, changes in axonal integrity, lower packing density of fibres or more obliquely oriented fibres. However, higher FA and lower MD localized in frontotemporal WM, where fibres of several tracts (IFO, inferior longitudinal fasciculus, uncinate fasciculus) are crossing (Mori *et al.*, 2005), might rather be the result of less fibre crossings in this area. While higher FA in fibre tracts usually correlates with higher structural integrity, this correlation may not be correct in brain areas containing a particular high amount of fibre crossings, which results in lower FA values. In these areas, a higher number of fibres and thus a larger number of fibre crossings may result in higher connectivity of the involved brain areas and thus may lead to lower FA (Beaulieu, 2002). This may explain increased FA in patients with ADHD in frontotemporal WM clusters. In this context, it has to be mentioned that age effects on FA and MD have been previously described in healthy adults (Sullivan & Pfefferbaum, 2006), although age effects are unlikely to account for the observed group differences in our study, because both groups did not differ significantly in age.

Conclusion

Taken together and in light of previous neuroimaging studies, our finding of orbitofrontal WM changes in adult patients with ADHD supports the notion of disturbed frontal-striatal circuitry in ADHD. DTI measures for WM integrity are in part directly correlated with impulsivity in this network, while attentional performance in patients with ADHD is correlated with microstructural properties in parts of the right SLF. Moreover, we provide further evidence for microstructural abnormalities in adult patients with ADHD in the cingulum bundle. Further studies combining refined functional and structural imaging methods are needed to investigate disturbed connectivity and their impact on behavioural measures in adult ADHD.

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Abbreviations

ACB, anterior cingulum bundle; ACC, anterior cingulate cortex; ADHD, attention deficit hyperactivity disorder; AVLT, Auditory-Verbal Learning Test; BADDS, Brown Attention-Deficit Disorder Scale for Adults; BPD, borderline personality disorder; CC, corpus callosum; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFO, inferior frontooccipital fasciculus; IQ, intelligence quotient; LPS, *Leistungspruefsystem;* MD, mean diffusivity; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; RT, reaction time; SLF, superior longitudinal fasciculus; TMT, Trail Making Test; TOVA, Test of Variables of Attention; WCST, Wisconsin Card Sorting Test; WM, white matter; WMS-R, Wechsler Memory Scale-Revised; WURS-k, Wender Utah Rating Scale.

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