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White-matter abnormalities in Tourette syndrome extend beyond motor pathways

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ABSTRACT

Tourette syndrome is a neuropsychiatric disorder with the cardinal symptoms of motor and vocal tics. Often tics are accompanied by comorbidities such as obsessive–compulsive disorder, attention-deficit–hyperactivity disorder or depression. Research has mainly focused on the cortico-striato-thalamo circuit, but clinical symptoms and recent neuroimaging studies reporting altered resting network connectivity have suggested abnormalities in Tourette syndrome beyond the major motor circuits.

We acquired diffusion-weighted data at 1.5 T in nineteen adult patients fulfilling the DSM-IV-TR criteria for Tourette syndrome and in a healthy control group.

Diffusion tensor imaging (DTI) analysis in our adult TS sample shows a decrease of FA and increase in radial diffusivity in the corticospinal tract. There are widespread changes (reduced FA and increased radial diffusivity) in the anterior and posterior limb of the internal capsule. Furthermore, it confirms prior findings of altered interhemispheric connectivity as indicated by a FA-decrease in the corpus callosum. In addition, our results indicate that TS is not restricted to motor pathways alone but affects association fibres such as the inferior fronto-occipitalis fascicle, the superior longitudinal fascicle and fascicle uncinatus as well.

Tics are the hallmark of Tourette syndrome, so the involvement of the corticospinal tract fits in well with clinical symptoms. Cortical regions as well as limbic structures take part in the modulation of tics. Our findings of alterations in long association fibre tracts and the corpus callosum are a potential source for hindered interhemispheric and transhemispheric interaction. The change in radial diffusivity points toward a deficit in myelination as one pathophysiological factor in Tourette syndrome.

Introduction

Tourette syndrome (TS) is a developmental neuropsychiatric disorder with the cardinal symptoms of motor and vocal tics. Often tics are accompanied by comorbidities such as obsessive–compulsive disorder (OCD), attention-deficit–hyperactivity disorder (ADHD) or depression. A "pure" Tourette syndrome without any comorbidity occurs in only ~10% of patients (Freeman et al., 2000; Khalifa and von Knorring, 2005). Its clinical course is characterized by the waxing and waning of symptoms (Leckman, 2003; Singer, 2005). The onset occurs during childhood; many patients experience a subsequent reduction of tic frequency and severity suggesting that the pathways involved play a significant developmental role. Research on Tourette syndrome has focused on the volumes of the basal ganglia and the cortico-striato-thalamo-cortical circuitry in terms of the underlying pathophysiological brain circuit (Singer, 2005; Saka and Graybiel, 2003; Albin and Mink, 2006; Leckman et al., 2006).

Several decades of investigation have confirmed a substantial genetic contribution of Tourette syndrome, but Tourette syndrome is a genetically heterogeneous disorder, probably involving multiple alleles at different loci. Genetic mutations, e.g. such as in Slit and Trk-like family member 1 (SLITRK1) are discussed in terms of playing a role in the pathophysiology of Tourette syndrome, but findings for the SLITRK1 gene in Tourette syndrome are heterogeneous (Abelson et al., 2005; Scharf et al., 2008; Miranda et al., 2009). Neuroimaging studies in Tourette syndrome have reported reduced caudate nucleus volumes (Peterson et al., 2003), altered volumes (smaller in children with Tourette syndrome, larger in adults with Tourette syndrome) of the total corpus callosum (Plessen et al., 2004) and thinning of

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sensorimotor cortices (Sowell et al., 2008). Church et al. (2009) measured immature and anomalous patterns of functional connectivity via resting-state functional magnetic resonance imaging (fMRI). They reported widespread abnormal connectivity patterns with the most prominent deficits in the Tourette syndrome group between the middle cingulate cortex, the dorsolateral prefrontal cortex and the inferior parietal lobe (Church et al., 2009). In an event-related fMRI study Bohlhalter et al. (2006) identified a network consisting of anterior cingulate and insular cortex, supplementary motor area and parietal operculum as being predominantly activated before tic onset.

In summary, in the literature on the pathophysiology of the Tourette syndrome two principles emerge: one is the alteration of basal ganglia volumes and the other is an altered connectivity pattern.

In order to investigate whether white-matter abnormalities contribute to these dysfunctional connectivity patterns in Tourette syndrome, a non-invasive, robust imaging method is needed.

Diffusion tensor imaging (DTI) answers this need. Fractional anisotropy is very sensitive to microstructural tissue organization, but it is not a specific marker for a certain pathophysiologic mechanism (Basser, 1995; Basser and Jones, 2002). Axial diffusivity λ_1 (diffusivity parallel to the principle axis of the fibre) and radial diffusivity $\lambda_{23} = (\lambda_2 + \lambda_3)/2$ (diffusivity perpendicular to the principle axis of the fibre) contribute valuable information (Hasan, 2006; Alexander et al., 2007). Results from animal research suggest that radial diffusivity is modulated by myelin in white matter (Tyszka et al., 2006; Song et al., 2005), whereas axial diffusivity might be more specific to axonal degeneration (Song et al., 2003). These measures have been obtained in mice with MRI at high field strength and their translation to human data is a matter of ongoing research (Xu et al., 2008; Qiu et al., 2008).

Based on DTI, Smith et al. (2006) developed tract-based spatial statistics (TBSS). TBSS aims to improve the sensitivity, objectivity and interpretability of the analysis of multi-subject diffusion imaging studies. In contrast to voxel-based morphometry (VBM) -style analysis, TBSS takes advantage of the spatial determinants of major white-matter tracts and thereby minimizes registration errors, thus eliminating the need for arbitrary smoothing.

In the current study where TBSS is applied to adult patients, we investigate which white-matter tracts show abnormalities in Tourette syndrome. We hypothesize that the microstructural organization is altered and aim to describe these change via FA, MD and axial as well as radial diffusivity. Given the cardinal symptoms of tics we hypothesized an impairment of the main motor tracts. Given the impaired resting networks as described by Church et al. (2009) and the modulation of tics by cortical areas (Stern et al., 2000; Bohlhalter et al., 2006; Kawohl et al., 2008; Peterson et al., 1998), we hypothesize that the white-matter changes would extend beyond motor regions and also implicate commissural and association fibres.

Methods

Data acquisition

Diffusion-weighted data and high-resolution 3-dimensional T1-weighted images were acquired for each subject on a 1.5 T scanner (SonataVision, Siemens) with an 8-channel phased array head coil and maximum gradient strength of 40 mT/m.

The diffusion-weighted data were acquired using a twice-refocused spin-echo diffusion-weighted echo-planar imaging (EPI) sequence with the following parameters: 2 mm slice thickness, no inter-slice gap, repetition time (TR) = 11,000 ms, echo time (TE) = 89 ms, field-of-view 256×208 mm^2, imaging matrix = 128×104, 71 transverse slices without an inter-slice gap. After an acquisition without diffusion weighting ($b = 0$ s/mm^2), images were acquired with diffusion gradients ($b = 800$ s/mm^2) applied in 30 non-collinear directions equally distributed on a sphere. The time required for a single acquisition was 407 s. The acquisitions were repeated three times in order to improve signal to noise ratio. T1 data were acquired using the standard Magnetization-Prepared, Rapid Acquisition Gradient-Echo (MP-RAGE) sequence: TR = 2200 ms, inversion time (TI) = 1200 ms, TE = 3.93 ms, field-of-view = 256×256 mm^2, imaging matrix = 256×256, number of slices = 128, flip angle = 15°, slice thickness = 1 mm, 1 acquisition = 9:38 min.

Data analysis

Patients and controls — data quality assessment

Twenty-eight adult patients (8 female, 20 male, aged 18–55 years) fulfilling the DSM-IV-TR criteria for Tourette syndrome participated in the study. For all participants the study protocol included a detailed standardized psychiatric and neurological evaluation by a board certified (neurology and psychiatry) physician (I.N.), a physical examination, and a neuropsychological assessment. This included the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), the Symptom Checklist 90-R (SCL90R, Derogatis et al., 1976) and the Barratt Impulsiveness Scale (BIS, 10th edition, Barratt, 1965). Psychiatric evaluation included assessment of comorbidities such as ADHD, OCD and depression according to DSM-IV-TR criteria. Control subjects were recruited from employees of the Research Centre Juelich and students from the RWTH Aachen University. Intake of any medication or current psychiatric or neurological disorder or a history of it were exclusion criteria. In accordance with institutional procedures, approval for the study was obtained from the Institutional Review Board. All subjects gave prior written informed consent.

Systematic differences due to movement artefacts could cause lower anisotropy indices in the TS group. To avoid that, the quality of the FA maps was assessed visually by two authors (Y.K, T.S) blind to the identity and group affiliation of controls and patients. Each data set was rated according to how clear-cut and detailed the structure of the FA map was identifiable (Smith et al., 2004). FA maps were rated ranging from “excellent” to “high” to “low” quality. After quality assessment data sets were identified and assigned to the control or patient group. Data sets of 14 patients and 14 controls were rated as “excellent” quality and five each as “high” quality.

Based on data quality analysis we included datasets of 19 patients (6 women, 13 men) aged 18–55 (mean 30.05 years, standard deviation (SD) 10.78) and 19 age-matched controls (7 women, 12 men, aged 20–50 years, mean age 28.89 years, SD 8.54). Demographic and clinical data from the patient group are summarized in Tables 1 and 2. Out of the 19 patients no patient reported at the time of measurement self injurious behaviour (SIB). SIB ever in life time was reported by 1 male patient, number 15 in Table 1.

In order to determine a potential influence of comorbidity in Tourette syndrome, data from one subsample of patients (4 women, 11 men) aged 18–48 (mean 29.4 years, SD 9.85) with no comorbidity were compared to an age-matched healthy control group (5 women, 10 men aged 20–43 (mean 28.2 years, SD 7.55).

Data analysis: TBSS approach in FSL

Data analysis was performed in FSL (FMRIB's (Functional magnetic resonance imaging of the brain) Software Library, www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). Data from 3 acquisitions were averaged and then corrected for EPI distortions and subject motion effects by using affine registration to the non-diffusion volumes implemented in the FMRIB's Diffusion Toolbox (FDT) (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). Non-brain voxels were extracted using the Brain Extraction Tool (BET) (Smith, 2002). FA, MD, eigenvalues and eigenvectors were calculated using FDT. Eigenvalues of the diffusion tensor matrix (λ_1, λ_2, λ_3) were used to obtain axial diffusivity λ_1 and radial diffusivity $\lambda_{23} = (\lambda_2 + \lambda_3)/2$. Voxel-wise statistical analysis of the FA data was carried out using

Table 1
Sociodemographic and clinical data of Tourette's patients.

Tourette patients ID	Age (years)	Sex	YGTTS total	YGTTS motor (MT)	YGTTS vocal (VT)	Social impairment	Current medication daily doses[a]	OCD	ADHS
1	31	M	67	14	13	40	Trimipramine 100 mg	No	No
2	20	M	40	11	9	20	10 mg escitalopram	No	No
3	23	F	57	15	12	30	None	No	No
4	44	M	59	14	5	40	200 mg tiapride	No	No
5	55	F	63	16	7	40	40 mg citalopram 400 mg carbamazopine	Yes	No
6	46	F	46	10	6	30	None	No	No
7	27	M	57	16	11	30	None	No	No
8	48	M	37	11	6	20	None	No	No
9	24	M	2	2	0	0	None	No	No
10	20	M	49	14	15	20	None	No	No
11	26	M	63	12	11	40	None	Yes	Yes
12	24	M	66	13	13	40	20 mg citalopram 200 mg tiapride, incompliant	No	No
13	22	F	37	10	7	20	Aripiprazole 10 mg Fluoxetine 20 mg	No	No
14	18	M	60	15	15	30	Ziprasidone 80 mg	No	No
15	21	M	77	18	9	50	Pimozide 4 mg, incompliant	Yes	Yes
16	35	M	68	15	13	40	None	No	No
17	33	F	43	8	15	20	Pimozide 2 mg	No	No
18	28	F	53	9	14	30	20 mg citalopram 50 mg methylphenidate	Yes	Yes
19	26	M	44	14	0	30	Trimipramine 50 mg	No	No

Abbreviations: f = female, m = male, YGTSS = Yale Global Tic Severity Scale — Total Score, OCD = obsessive–compulsive disorder, ADHS = attention-deficit–hyperactivity syndrome, BIS = Barratt Impulsiveness Scale — Total Score.
[a] Out of the unmedicated patients all except one were medication naive. She had taken aripriprazole 12 weeks prior to study for 3 weeks 5 mg/day.

Tract-Based Spatial Statistics (TBSS) implemented in FSL (Smith et al., 2006).

First, all individual FA maps were registered to each other to determine the study-specific target which was identified as an image which minimizes the amount of warping required for all other subjects to align to it. After target identification, all other FA images were aligned to it using a non-linear registration algorithm and then transformed into $1\times1\times1\,mm^3$ Montreal Neurological Institute (MNI152) space. All subsequent processing was carried out using this space and resolution.

Then, the mean of all aligned FA images was created and thinned to generate a mean FA skeleton, which represented the centre of all tracts common to the group. A threshold of the mean FA skeleton image >=0.2 was applied to the skeleton to exclude voxels which are grey matter or CSF in the majority of subjects. Then, the aligned FA data of each subject were subsequently projected (perpendicular to the local tract direction) onto this skeleton by searching for the local centre of the nearest relevant fibre tract.

Thus, for each subject an individual FA skeleton was produced that was analyzed in a group comparison of patients versus controls using FSL "Randomize" with 6500 permutations. "Randomize" (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl/) uses a permutation based statistical inference that does not rely on a Gaussian distribution (Nichols and Holmes, 2002). Gender was included as covariate. All voxel-wise group comparisons were performed using two-sample unpaired *t*-tests. TBSS analyses of MD, radial diffusivity and axial diffusivity were performed in the same manner.

A statistical threshold $t>3$, $P<0.05$, corrected for multiple comparisons with Threshold-Free Cluster Enhancement (TFCE) was used for this analysis. TFCE helps one to identify cluster-like structures in images without definition of an initial cluster-forming threshold or carrying out a large amount of data smoothing (Smith and Nichols, 2009).

Identification of the abnormal white-matter (WM) tracts revealed by TBSS was based on the Johns Hopkins University (JHU) – ICBM-DTI-81 white-matter labels atlas and the white-matter tractography atlas (Wakana et al., 2004; Hua et al., 2008). TBSS results of MD, radial diffusivity and axial diffusivity were analyzed in the same manner.

Table 2
Symptom check list scores (SCL 90R) and Barratt Impulsiveness Score ($n=19$).

Symptom check list	Tourette syndrome
SCL-90R (*t*-value)	mean (SD)
Somatization	56.8 (12)
Obsessive–compulsive	65.3 (10)
Interpersonal sensitivity	66.5 (13.5)
Depression	61.7 (11.5)
Anxiety	61.3 (12.1)
Hostility	62.7 (9.7)
Phobic anxiety	59.9 (13.8)
Paranoid ideation	65.3 (9.3)
Psychoticism	62.2 (8.7)
Global severity index	66.5 (10.0)
Positive symptom total	63.4 (7.9)
Positive symptom distress index	63.3 (11.1)
Barratt Impulsiveness Score	81.6 (10.9)

BIS normative values: Patton et al. (1995) (63.4 ± 10.1), Fossati et al. (2001) (59.2 ± 7.3).

Data analysis: correlation of behavioural data with diffusion indices

In addition we performed correlations between diffusion indices in regions-of-interest based on the significant group results. Region-of-interest masks ($n=11$) were created in FSL based on the JHU White-Matter Tractography Atlas. In FSL these masks were overlaid on the TBSS results. Within each mask the mean FA-value (or mean axial or radial diffusivity value) was calculated in Matlab (MATLAB, The MathWorks). These mean values were correlated with the behavioural data (=YGTTS scores) using Spearman rank correlation coefficient ($P<0.05$ uncorrected for multiple comparisons) for the whole patient group and for the subsample without comorbidities.

Results

Whole group — TBSS results

Patients with Tourette syndrome in comparison to healthy controls showed a significant reduction of FA in the corticospinal

tract, the corpus callosum and long association fibre pathways such as the inferior fronto-occipital fascicle and the superior longitudinal fascicle as well as in the uncinate fascicle. The coordinates of the local maxima are listed in Table 4. Reductions in FA are displayed in Fig. 1. The FA reduction in the internal capsule is displayed in detail in Fig. 2.

Significant changes of radial diffusivity were detected but not for MD and axial diffusivity. An increase in radial diffusivity was detected in patients in the corpus callosum (MNI −1/11/20 body corpus callosum, MNI 12/−37/20 splenium corpus callosum), corticospinal tract MNI (−20/−30/42), and superior corona radiata (MNI −19/−29/39). FA decreases are compared to increased radial diffusivity in Fig. 3.

TS "only" — TBSS results

The subsample of Tourette patients with no comorbidities showed in contrast to healthy controls, reduced FA-values in the corpus callosum (MNI −2/11/21 body corpus callosum, MNI −7/−6/27 body corpus callosum, MNI 1/9/22 body corpus callosum, MNI 14/−35/23 splenium corpus callosum) (FWE corrected, $P<0.05$).

Correlations between diffusion indices and YGTTS scores

There was no significant correlation between FA-values, radial or axial diffusivity and YGTTS scores in the whole group.

In the subgroup without comorbidities (TS "only") FA-values of the right corticospinal tract, the right and left uncinate fascicle and the right cingulum correlated significantly with the motor subscore of the YGTTS scale.

FA-values of the right and left anterior thalamic radiation, forceps minor and the right and left uncinate fascicle correlated significantly with the YGTTS sum of motor and vocal tics (MTVT). FA-values of the cingulum correlated significantly with the total sum of the YGTTS. Correlations coefficients and *P*-values are summarized in Table 3. Correlations for FA-values in the right corticospinal tract and motor tics as well as for FA-values in the forceps minor with motor and vocal tics are displayed in Figs. 4a and b, respectively. When performing multiple (n) tests each at an individual type I error rate of \alpha, then the chance of at least one test being significant by chance is no longer \alpha, but $1-(1-\alpha)^n$ (Perneger, 1998).

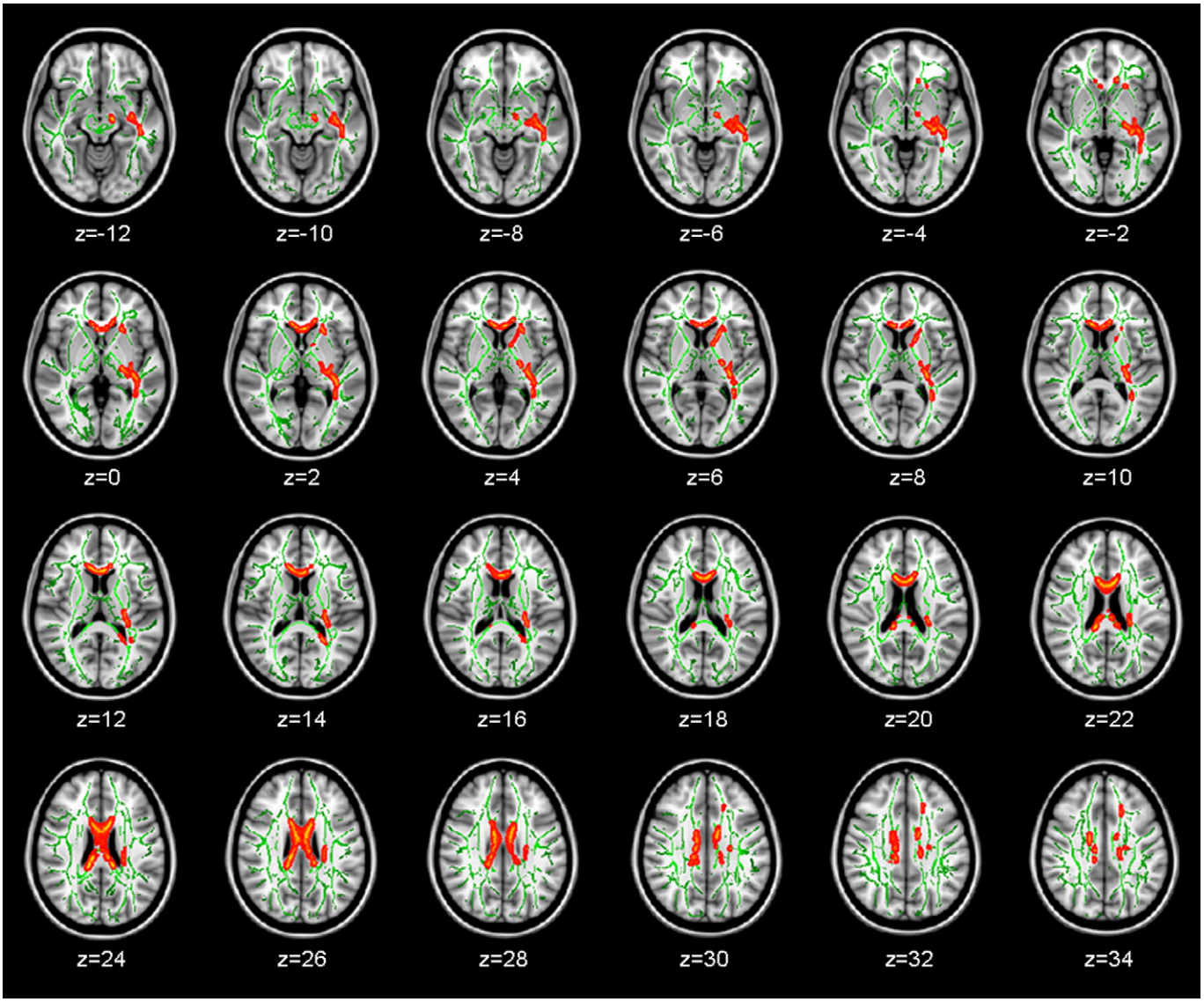

Fig. 1. Axial images demonstrating regions of significantly decreased FA (red) in Tourette patients. Background: mean tract skeleton (green) and MNI 152 brain. Changes are spread over different brain areas and systems. The white-matter microstructure is altered in the anterior and posterior limb of the internal capsule, the corpus callosum and long association fibres such as the superior longitudinal fascicle. For illustration purposes we used the tbss_fill option provided by FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

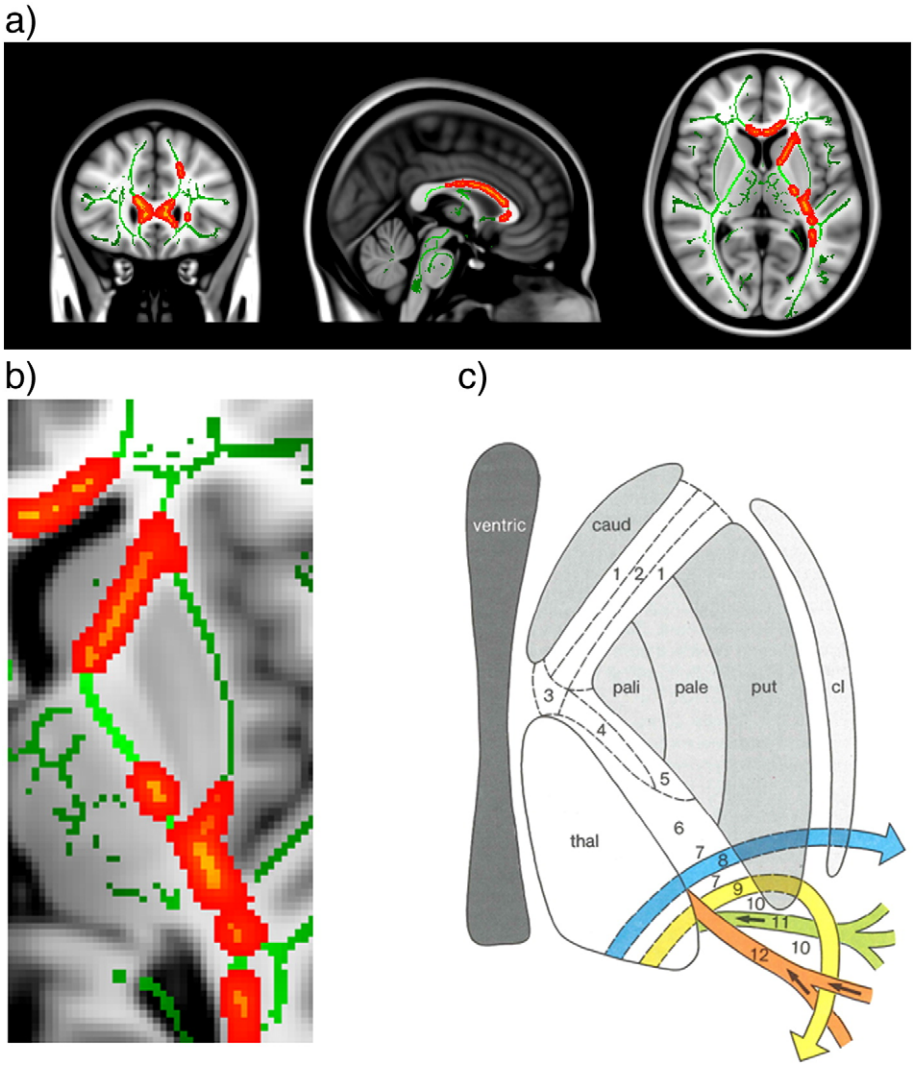

Fig. 2. a) Significantly reduced FA (red) in the anterior and posterior limb of corpus callosum and the internal capsule in patients in comparison with healthy controls. (MNI coordinates x = 1, y = 27, z = 6). For illustration purposes we used the tbss_fill option provided by FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). b) TBSS results of FA reduction in the internal capsule are zoomed out of Fig. 2a for a better comparison to an anatomic sketch of the internal capsule. For illustration purposes we used the tbss_fill option provided by FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). c) Anatomic sketch of the internal capsule (Zilles, 1987):

1. frontopontine tract
2. anterior thalamic peduncle
3. corticonuclear tract
4. corticospinal tract
5. corticorubral and corticotegmental tract
6. superior thalamic peduncle
7. inferior thalamic peduncle
8. acoustic pathway (blue)
9. visual pathway (yellow)
10. posterior thalamic peduncle
11. parieto-temporo-occipito-pontine fibres (green)
12. corticotectal and corticotegmental fibres (rot).

(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The other diffusion parameters MD, axial or radial diffusivity did not reach significance, neither in the whole patient group nor in the TS "only" group.

Discussion

DTI analysis in our adult Tourette syndrome patients shows a decrease of FA and increase in radial diffusivity in the corticospinal tract. There are widespread changes (reduced FA and increased radial diffusivity) in the anterior and posterior limb of the internal capsule. Furthermore, a FA-decrease in the corpus callosum in combination with increased radial diffusivity indicates altered interhemispheric connectivity via the corpus callosum. In addition our results indicate that TS is not restricted to motor pathways alone but affects association fibres such as the inferior fronto-occipitalis fascicle, the superior longitudinal fascicle and fascicle uncinatus as well.

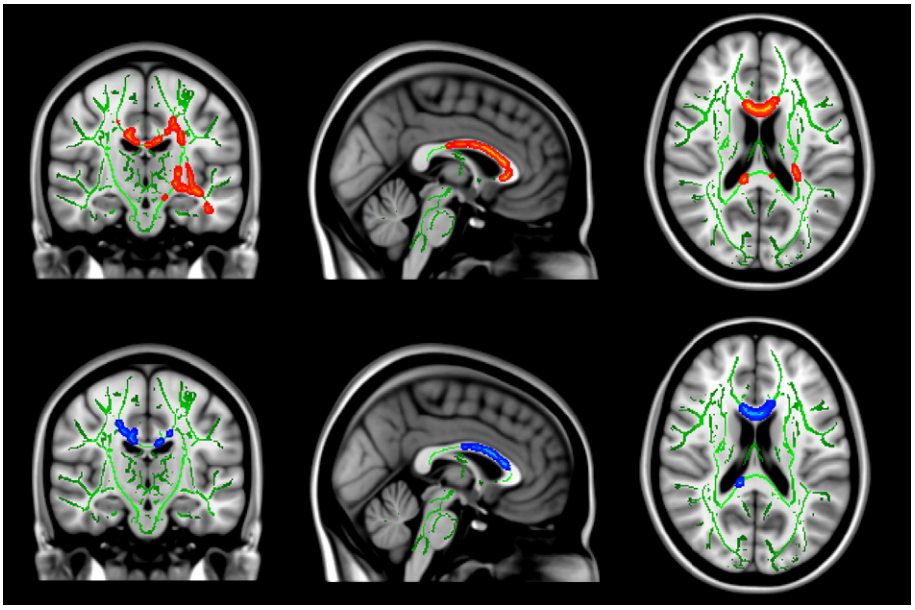

Fig. 3. FA reductions in Tourette patients are displayed in the upper row in red. Alterations overlap to a large degree with the increases in radial diffusivity which are depicted in blue in the lower row. Background: mean tract skeleton (green) and MNI 152 brain. (MNI coordinates: x = −1, y = −17, z = 19) For illustration purposes we used the tbss_fill option provided by FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

TBSS results — corticospinal tract and internal capsule anterior and posterior part

Tics are the hallmark of TS. It is intuitive, therefore, to study the main motor pathway, the corticospinal tract. Differences in structural white-matter microrganization start in the superior corona radiata and continue to the anterior thalamic radiation. At the brainstem level, the cortical spinal tract seems also to be affected. However, at the brainstem level one has to interpret results with caution since white matter is closely embedded in grey matter. In agreement with our hypotheses the corticospinal tract as main motor pathway is affected in TS (Table 4).

The affection of the anterior limb of the internal capsule corresponds well with positive results from deep brain stimulation in TS with electrodes positioned there (Flaherty et al., 2005; Neuner et al., 2009). In the anterior limb FA alterations might affect the frontopontine tract which carries the motor pathways from the frontal lobe to the pons. In addition we found FA reduction in the anterior thalamic peduncle which connects the medial thalamic nuclei with the rostral part of the frontal lobe and the cingulate cortex.

These altered connections to prefrontal and frontal areas are clinically important. The complex interaction between basal ganglia and the prefrontal and frontal projections is one pathophysiologic key mechanism in Tourette syndrome (Singer, 2005; Bohlhalter et al., 2006; Marsh et al., 2007). Patients are able to suppress tics for a certain time — to what extent is highly variable. Activities which require focused attention such as software development or driving

Table 3
Significant correlations between FA-values and YGTTS scores ($n = 13$, "TS only").

White matter	YGTTS score*	Correlation coefficient r	P-value
Anterior thalamic radiation	MTVT	R 0.57, L0.64	R0.04, L0.02
Corticospinal tract R	MT	0.57	0.04
Uncinate fascicle	MTVT	R0.6L 0.58	R0.03, L0.05
Uncinate fascicle	MT	R0.59L 0.56	R0.03, L0.05
Forceps minor	MTVT	R 0.65	0.02
Forceps minor	MT	R0.67	0.01
Cingulum R	Total YGTTS	0.55	0.05

MT = motor tics, VT = vocal tics, MTVT = motor and vocal tics YGTTS subscore, R = right, L = left.

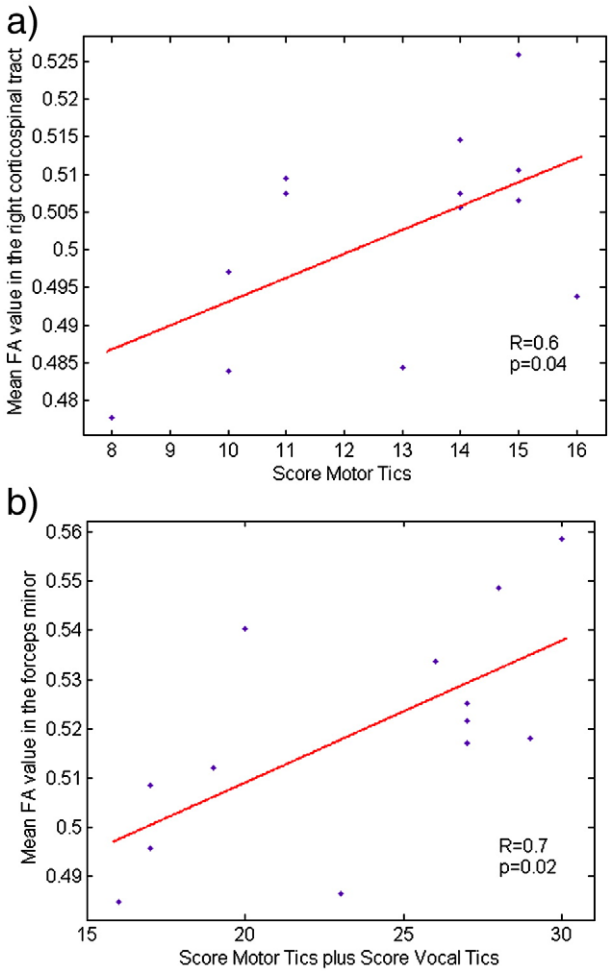

Fig. 4. a) Significant correlation between FA-values in the right corticospinal tract and the motor tic score in the subsample of Tourette patients without comorbidities. b) Significant correlation between FA-values in the forceps minor and the motor and vocal tic score in the subsample of Tourette patients without comorbidities.

Table 4
FA-changes Controls vs. Tourette's patients ($n = 19$, whole group), family-wise error (FWE) corrected, $P<0.05$.

MNI coordinates X Y Z local maxima	Anatomic region (JHU white matter atlas)	Anatomic tract (JHU white-matter tractography atlas)
−8 15 20	Body corpus callosum	Forceps major
−2 9 22		
−2 11 21		
9 −4 27		
−25 −51 12		
−15 −31 28	Splenium corpus callosum	Forceps major
−12 −34 24		
−14 −36 23		
−10 −32 22		
−23 22 2	Superior corona radiata L	Inferior fronto-occipital fascicle L, Uncinate fascicle L
−20 −29 41	Superior corona radiata L	Corticospinal tract L,
−20 −34 44		Anterior thalamic radiation L,
−20 −31 42		Cingulum L
−33 −14 −6	External capsule L	Inferior fronto-occipital fascicle L
−32 −16 −4		Superior longitudinal fascicle (temporal part) L
−33 −19 −3		Superior longitudinal fascicle L
−33 −11 −8		Uncinate fascicle L
−17 12 6	Anterior limb of internal capsule L	Anterior thalamic radiation L
−19 15 6		Inferior fronto-occipital fascicle L
−20 19 6		Uncinate fascicle L
−15 8 6		
−21 21 3		
−27 −25 11	Retrolenticular part of internal capsule L	Corticospinal tract L Superior longitudinal fascicle L
−34 −46 6	Posterior thalamic radiation L	Inferior fronto-occipital fascicle L,
−34 −53 8		Inferior longitudinal fascicle L
−36 −45 2		Superior longitudinal fascicle (temporal part) L
−36 −50 2		Superior longitudinal fascicle L
−12 −13 −14	Cerebral peduncle L	Corticospinal tract L

will also result in a marked tic reduction. The anterior part of the cingulate cortex has been shown to be activated during tic suppression (Peterson et al., 1998; Kawohl et al., 2008), but also prior to tics (Bohlhalter et al., 2006) and during tics (Stern et al., 2000). Using magnetization transfer imaging (MTI), Müller-Vahl et al. (2009) reported a negative correlation between tic severity and orbitofrontal structures, the right cingulate gyrus and parts of the parietal–temporal–occipital association cortex bilaterally.

As shown in Fig. 2, the decrease in FA is not limited to the anterior part of the internal capsule but affects the posterior limb as well. Here, as Figs. 2b and c indicate it could affect the inferior, superior and posterior thalamic peduncle (Zilles, 1987). The inferior thalamic peduncle hosts fibres of the visual and acoustic pathway and connects the anterior thalamic nuclei with the retrosplenial region of the cingulate cortex. This might result in an altered filtering of incoming stimuli resulting in a modulation of tic frequency or intensity. The superior thalamic peduncle connects the pre- and postcentral gyrus with the neighbouring prefrontal and parietal cortex and the ventrocaudal nucleus of the thalamus. This disturbed connection might give rise to the premonitory sensations which Tourette patients often describe. Thomalla et al. (2009) described white-matter changes below the postcentral cortex and associate them with premonitory urges. In opposite to our TBSS study they describe a regional increase of FA below the somatosensory cortex. However, the interesting study of Thomalla et al. and our data are difficult to compare for the following reasons: first, there are profound technical differences in data acquisition (3 T scanner vs 1.5 T scanner, sequence parameters ($b = 1000$ vs. 800, 6 vs. 30 directions, 2 vs. 3 averages). Second the preprocessing and processing differs significantly (SPM2 vs. FSL, VBM approach including 8 mm smoothing vs. TBSS approach with no smoothing). Further MR-studies with more comparable technical prerequisites and detailed DTI measures (e.g. axial and radial diffusivity) are needed to replicate findings.

The posterior thalamic peduncle connects cortical association areas to the pulvinar thalami, the area pretectalis, the tectum, the nucleus ruber and the substantia nigra. Via these connections stimuli from the environment could possibly modify the input in the cortico-striato-thalamo circuit and ergo alter the tic type or tic frequency. Furthermore the corticorubral and corticotegmental fibres which connect Brodmann area 6 to the nucleus ruber and the tegmentum are affected by FA decreases. This is a further connection able to modify cortical motor signals.

At a corrected P-value of 0.05 these results are limited to the left side. This is no longer the case at thresholds of $P<0.001$ or 0.005 uncorrected. We therefore discuss this finding as a result of low statistical power due to the reduced sample size.

TBSS results — commissural fibres

The corpus callosum transfers information between the hemispheres, takes part in the modulation of attention (Hugdahl, 1998), inhibition of cortical activity (Boroojerdi et al., 1999) and plastic reorganization of the brain (Werhahn et al., 2002). The corpus callosum is supposed to play an important role in modulation of tics by mediating the inhibiting influence by prefrontal cortices (Peterson et al., 1998; Plessen et al., 2004). The reduced FA-values and increased radial diffusivity in the corpus callosum in our data could be responsible for a diminished inhibitory influence.

Plessen and colleagues reported two studies concerning the role of the corpus callosum in Tourette syndrome (Plessen et al., 2004; Plessen et al., 2006). They investigated the size of the midsagittal corpus callosum in structural T1-weighted MR-images in 158 individuals ranging from 5–65 years (Plessen et al., 2004). Concerning the size the key finding was that in children with Tourette syndrome the corpus callosum size was smaller in comparison to controls whereas in adults with Tourette syndrome it was larger. These findings replicated earlier studies in children by Peterson et al. (1994) and in adults by Moriarty et al. (1997). The second study by Plessen and colleagues investigated via diffusion-weighted MR-images the FA-values in the corpus callosum in children with Tourette syndrome. They found in all sub-regions of the corpus callosum (Plessen et al., 2004) a reduced FA-value. Our adult sample shows reduced FA-values

in the corpus callosum. Regions with decreased FA-values overlap in our data with areas of increased radial diffusivity. This could be e.g. explained by a dysregulation in myelination. The described increased radial diffusivity in the corpus callosum in our adult patient sample is in line with our hypothesis of affection of commissural fibres in Tourette syndrome.

TBSS results — association fibre bundles

The modulation of tics by cortical activation depends not only on interhemispheric but also on long association fibre bundles within one hemisphere. Church et al. (2009) described altered connectivity patterns between the prefrontal, frontal, midcingulate cortex, the precuneus and the inferior parietal gyrus. Such networks could rely on long distance fibre bundles such as the superior longitudinal fascicle connecting all parts of the isocortex ranging from rostral to occipital. In agreement with our hypotheses that association fibre bundles are affected as well in TS the superior longitudinal fascicle, and the inferior fronto-occipital fascicle show a decrease in FA. Clinical observations show that tics are modulated in frequency and intensity by emotion. Functional magnetic resonance imaging (fMRI) data showed an amygdala hypersensitivity to emotional facial expressions in Tourette patients (Neuner et al., in press). The FA-decrease in the uncinate fascicle could be one component in addition to altered amygdala volumes (Amunts et al., 2007; Peterson et al., 2007) underlying the altered emotional perception in TS. This finding is in line with our hypothesis that alterations in white matter in Tourette syndrome would reach beyond the motor system.

Dysregulation in myelination as a potential pathophysiological mechanism

Our findings associate widespread white-matter changes with Tourette syndrome. The alterations are not limited to one system or one brain area. It is, however, unclear in which time window of brain development and maturation these changes occur — probably based on a genetic background with environmental factors on top (Singer, 2005; Leckman et al., 2006; Neuner and Ludolph, 2009). According to our aim to describe the white-matter changes in terms of axial and radial diffusivity in addition to FA, the increased radial diffusivity helps to identify a potential pathophysiological mechanism in TS. Increased radial diffusivity could indicate less myelination or reduced oligodendroglial integrity (Cheong et al., 2009). As shown in Fig. 3, areas of reduced FA-values overlap to a large degree with areas of increased radial diffusivity. In a mice model Stillman et al. (2009) describe a genetically regulated expression pattern in projection neurons of the cortico-striato-thalamo-cortical circuit. What genetic loci are involved in the pathogenesis of Tourette syndrome is a focus of ongoing research (Leckman et al., 2006; Neuner and Ludolph, 2009).

In the patient group without comorbidities the findings in the corpus callosum show also a decrease in FA and an increase in radial diffusivity. Therefore, the deficient myelination in the corpus callosum is a key finding in our data linked with Tourette syndrome itself and not with the comorbidities. In the TS "only" subgroup (e.g. no comorbidities) the motor tic score correlated significantly with the FA-changes in the anterior thalamic radiation, the right corticospinal tract, the right and left uncinate fascicle and the forceps minor. Yet, interpreting these results one has to keep in mind that the correlations were not corrected for multiple comparisons.

Our study is a cross-sectional study in adults patients were tics persisted into adulthood. There are several mechanisms influencing the FA-value in Tourette syndrome. One factor could be deficient myelination during brain maturation e.g. on a genetic background. To a varying degree during the course of the disorder compensatory mechanisms e.g. more axonal pruning could result in an increasing FA-value. But this compensation attempt is still insufficient on a structural level in comparison to healthy controls as shown by the lower FA-value for the patients in comparison to controls. It is also falls short on a functional level as the correlation data show. Patients with higher FA-values within the patient group suffer more tics.

Longitudinal studies in Tourette syndrome starting in childhood and following up patients into adulthood would answer various important questions regarding the primary pathophysiological mechanism and structural/functional changes due to adaption and compensation.

TS patients can suppress tics for a certain time, varying from individual to individual and actions such as software development or driving which require focused attention can result in a marked tic reduction. The prefrontal cortices and the cingulum have been shown to be activated during tic suppression (Peterson et al., 1998; Kawohl et al., 2008), the cingulum also prior to tics (Bohlhalter et al., 2006) and during tics (Stern et al., 2000). Different levels of capacity for adaption and compensation between the whole patient group and the TS "only" group may account for the lack of correlations between YGTTS scores and FA-values in the whole group.

Limitations of the study

The sample size for data analysis was decreased to 19 patients. This percentage is comparable to other groups studying Tourette syndrome (Hampson et al., 2009). This down sampling prevented a segregation of non-medicated patients, patients without comorbidities and the segregation of patients according to sex into subgroups with sufficient statistical significance in the DTI analysis. Excluding patients with comorbidities, one risks omitting important pathophysiologic components of Tourette syndrome. Neuroleptic medication has been reported to have an impact on basal ganglia size (Scherk and Falkai, 2006). Thus, an influence from sex, medication and comorbidities cannot be excluded. It is a limitation of this study that no specific tests for comorbidities such as ADHS, OCD, depression and anxiety have been used. As the YGTSS scores indicate, we have included severely affected patients in our study. As such, the composition of the patient group included for data analysis is a compromise. This is a compromise most groups studying Tourette syndrome face and they report data from TS samples including medication and comorbidities (Hampson et al., 2009; Sowell et al., 2008; Bohlhalter et al., 2006; Plessen et al., 2004, 2006; Marsh et al., 2007; Stern et al., 2000). Plessen reported that in her samples comorbidities and medication did not show a significant influence (Plessen et al., 2004; Plessen et al., 2006). However, there are also studies focusing on TS "only" (Müller-Vahl et al., 2009; Thomalla et al., 2009) providing important data without potential confounds of medication, sex and comorbidities. Additional challenges for MR-imaging arise from this particular patient group. To account for the confounds due to movement we assessed the quality of our whole data sample blind to group affiliation. The TBSS approach is also limited to large fibre bundles which form the skeleton. However, in a movement disorder like Tourette syndrome this approach seems appropriate to reduce the risk reporting alterations which are in fact due to head motion.

The TBSS approach has also limitations in comparison to VBM-style approaches (Smith et al., 2006). If the tract width gets smaller than the original voxel size mutual FA-changes do not reflect truly altered FA-values but may result from a mix of grey and white tissue. Partly for this reason the FA skeleton is thresholded at an FA-value of 0.2. Another confound especially in a movement disorder is the within-scan head motion. We addressed this confound on one hand by modifying the MR-sequence, on the other hand we assessed the quality of the FA maps as suggested by Smith et al. (2004) by visual assessment blind to group affiliation. There is also a possibility that pathologies such as stroke or tumours reduce FA so strongly that

potential areas of interest are excluded from analysis. However, hypothesized changes in Tourette syndrome are far more subtle.

In summary, reduced FA and increased radial diffusivity as detected by DTI in adult Tourette syndrome patients affects different systems and brain regions. The pathologic pattern reaches beyond the corticospinal tract and affects interhemispheric connections such as the corpus callosum as well as intrahemispheric long association fibre tracts. For the motor system the correlations with the corticospinal tract and the anterior thalamic radiation indicate that reduced FA is of clinical relevance. The affection of limbic structures such as the uncinate fascicle and its close correlations with the motor and vocal tic score indicates that alterations in Tourette syndrome exceed motor pathways and also affect limbic structures.

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