Structural changes in the somatosensory system correlate with tic severity in Gilles de la Tourette syndrome

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Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterized by multiple motor and vocal tics. Previous structural MRI studies have identified regional abnormalities in grey matter, especially in the basal ganglia. These findings are consistent with the assumption of alterations in cortico-striato-thalamo-cortical circuits and dopaminergic neurotransmission playing a major role in the pathophysiology of GTS. Additionally, recent imaging studies suggested an involvement of sensory-motor cortices in the pathophysiology of GTS. However, little is known about the role of white matter changes in GTS. In this study, we aimed to examine whether GTS is associated with abnormalities in white matter microstructure and whether these changes are correlated with tic severity. In a morphometric study based on diffusion tensor MRI of the whole brain, we compared brain tissue diffusion characteristics between 15 unmedicated adults with GTS without psychiatric co-morbidity and 15 healthy age- and sex-matched controls. We performed voxel-based morphometry (VBM) of regional fractional anisotropy (FA) values to identify regional differences in white matter microstructure between the groups. We also tested for a linear relationship between regional FA values and clinical scores of tic severity. Probabilistic fibre tracking was applied to characterize anatomical connectivity of those areas showing differences in regional FA. Compared with healthy controls, GTS patients showed bilateral FA increases in white matter underlying the post- and precentral gyrus, below the left supplementary motor area, and in the right ventro-postero-lateral part of the thalamus. The peak increase in FA was located below the left postcentral gyrus. Probabilistic tractography identified transcallosal and ipsilateral cerebello-thalamo-cortical pathways of the somatosensory system passing through this subcortical region. In patients, regional FA in this region showed an inverse linear relationship with tic severity. These findings demonstrate, for the first time, structural alterations in somatosensory pathways in GTS. Changes of water diffusion characteristics point towards reduced branching in somatosensory pathways in GTS patients. The negative correlation between higher regional FA values and fewer tics...
suggests that these alterations of white matter microstructure represent adaptive reorganization of somatosensory processing in GTS.

Keywords: Gilles de la Tourette Syndrome; tics; diffusion tensor imaging; fractional anisotropy; somatosensory system

Abbreviations: ADHD = attention deficit hyperactivity disorder; BA = Brodmann area; CC = corpus callosum; CSF = cerebrospinal fluid; DCI = diagnostic confidence index; DTI = diffusion tensor imaging; DSM-IV-TR = Text Revision of the Diagnostic and Statistical Manual of Mental Disorders 4th edition; EPI = echo planar imaging; FA = fractional anisotropy; FDR = False Discovery Rate; FLAIR = fluid attenuation inversion recovery; FMRIB = Oxford Centre for Functional MRI of the Brain; FLIRT = FMRIB’s Linear Image Registration Tool; FSL = FMRIB Software Library; FWHM = full width at half maximum; GTS = Gilles de la Tourette syndrome; \( \lambda_1 \) = first eigenvalue; \( \lambda_2 \) = second eigenvalue; \( \lambda_3 \) = third eigenvalue; MINI = Montreal Neurological Institute; MRI = magnetic resonance imaging; MD = mean diffusivity; MRVS = Modified Rush Video Scale; OCD = obsessive-compulsive disorder; SPM = Statistical Parametric Mapping; TE = echo time; TI = inversion time; TR = repetition time; VBM = voxel-based morphometry; VL = ventral lateral thalamus; VOI = volume of interest; VPL = ventral posterolateral thalamus; YGSTSS = Yale Global Tic Severity Scale

Introduction

Gilles de la Tourette Syndrome (GTS) is characterized by chronic motor and vocal tics typically starting during childhood with a mean age of onset around the age of six (American Psychiatric Association, 2000; Leckman et al., 2001). Abnormal neuronal processing in cortico-striato-thalamo-cortical circuits and altered dopaminergic neurotransmission have been implicated in the pathophysiology of GTS (Stern et al., 2000; Peterson, 2001; Singer and Minzer, 2003; Singer, 2005; Mink, 2006). Post-mortem studies of single patients identified striatal and prefrontal dopaminergic abnormalities (Singer et al., 1991; Minzer et al., 2004) and changes in the distribution of inhibitory neurons in the striatum and globus pallidum (Kalanithi et al., 2005).

Apart from post-mortem studies, knowledge on structural pathology in GTS mainly relies on morphometric analyses of in vivo MRI data obtained in affected individuals (Peterson, 2001). Changes in regional volumes and signal have been reported in numerous brain regions with sometimes conflicting results in different studies. Some authors identified reduced volumes of the caudate and lentiform nucleus and globus pallidus (Peterson et al., 1993, 2003), while others reported unchanged basal ganglia volumes in children (Singer et al., 1993) or specifically girls with GTS (Singer et al., 2000). Additionally, a loss of the physiological asymmetry of the putamen (Singer et al., 1993) and caudate nucleus (Moriarty et al., 1997) was reported in GTS. Cortical regional abnormalities were also reported, including larger prefrontal and parieto-occipital regions in GTS patients (Peterson et al., 2001) and increased volumes of the hippocampus and amygdala (Peterson et al., 2007). Recently, cortical thinning in large areas of the frontal and parietal lobe has been demonstrated by high-resolution structural MRI in children with GTS (Sowell et al., 2008). Regarding white matter, a regional increase of right prefrontal white matter (Fredericksen et al., 2002), and a decrease of left deep frontal white matter were found in GTS patients (Kates et al., 2002). Additionally, altered white matter microstructure as possible evidence of reduced interhemispheric connectivity was demonstrated in the corpus callosum in children with GTS (Plessen et al., 2006). Whereas morphometric changes in basal ganglia volumes have been interpreted as a core abnormality in GTS probably related to the generation of tics (Peterson et al., 2003), changes in cortical regional volumes have been attributed to adaptive reorganization (Peterson et al., 2001, 2007). However, differences in image analysis and sample characteristics such as age, sex, co-morbidity and neuroleptic medication are likely to have influenced results of previous studies, so that these studies cannot easily be compared.

Tics are involuntary sudden stereotyped physiological movements or vocalizations. They can be simple or complex and typically wax and wane over time (Leckman et al., 2001). Although motor symptoms represent the hallmark of GTS, there is little doubt that tics are not a pure motor phenomenon. Tics are usually preceded by premonitory sensations, in particular the urge to move (Bliss, 1980; Bullen and Hemsley, 1983). Paralleling this clinical observation, there is growing experimental evidence of abnormal sensory-motor processing in GTS (Leckman et al., 1993; Nowak et al., 2005; Orth et al., 2005). Based on these observations, adaptive processes involving the somatosensory system have been postulated (Leckman et al., 1993; Kwak et al., 2003). However, evidence for structural changes in the somatosensory system is scarce.

Magnetic resonance diffusion tensor imaging (DTI) allows studying the water diffusion properties of tissue and by this provides clues on the microstructural organization of tissue. Anisotropy of water diffusion in tissue describes its property of being directionally dependent. In cerebral white matter, water diffusion is fast along the main fibre direction and slower perpendicular to it, resulting in anisotropic diffusion (Beaulieu, 2002). Therefore, DTI is particularly useful for in vivo studies of the cerebral white matter as it allows characterizing the organization and integrity of white matter pathways (Behrens et al., 2003b; Johansen-Berg and Behrens, 2006). By this, DTI can be used to study white matter abnormalities associated with specific pathological conditions, such as degeneration of white matter pathways or plastic changes of white matter organization occurring during the course of a disease (Johansen-Berg and Behrens, 2006). Diffusion properties of tissue can be characterized by different parameters. The diffusion tensor can be displayed as an ellipsoid, the principal axes of which are defined by the three mutually perpendicular eigenvectors. The three eigenvalues \( \lambda_1, \lambda_2, \lambda_3 \) represent the diffusivities along these main axes. They are sorted according to magnitude with \( \lambda_1 \) representing the highest and \( \lambda_3 \) representing the lowest diffusivity. The mean diffusivity (MD) represents orientationally averaged diffusion. Fractional anisotropy
(FA) is the most frequently used index of anisotropy in neuroimaging studies. It ranges from zero in fully isotropic diffusion to one in fully anisotropic diffusion (Beaulieu, 2002).

Here, we used DTI to address the question whether GTS is associated with microstructural changes in white matter organization. We avoided confounding effects of medication, age and co-morbidity by studying only unmedicated adult GTS patients without psychiatric co-morbidity. We compared diffusion properties of brain tissue of GTS patients as characterized by DTI with those of a healthy control group matched for age and gender. Our aim was to identify abnormalities in white matter structure, assign these changes to distinct sensory-motor pathways using fibre tracking, and to correlate regional abnormalities in white matter structure with tic severity. Given the early onset and chronicity of GTS and the sensory-motor nature of tics we made two predictions. We hypothesized that GTS is associated with structural changes in sensory-motor pathways and that these changes are associated with tic severity.

Material and methods

Subjects

Fifteen patients (13 men, mean age: 34.5 ± 8.9 years) were recruited from two specialized GTS outpatient clinics (Department of Neurology, University Hospital Hamburg and Clinic of Psychiatry, Hannover Medical School). We only included unmedicated GTS patients without psychiatric co-morbidity. Fifteen healthy subjects matched for age and gender served as a control group (13 men, mean age: 34.6 ± 9.1 years). All control subjects had a normal neurological and psychiatric examination and no history of neurological or psychiatric disorders. Handedness was assessed using the Edinburgh handedness inventory (Oldfield, 1971): one patient and one control subject were ambidextrous, the other participants were consistent right-handers. The study was approved by the local Ethics Committee (No. 2514) and written consent was obtained from all participants prior to the experiment according to the Declaration of Helsinki.

Clinical assessment

Each patient was clinically assessed by a neurologist or psychiatrist experienced in diagnosing and treating GTS. Lifetime clinical information was systematically collected using standardized clinical assessment and a semi-structured interview adapted from Robertson and Eapen (1996). In this interview, patients were systematically asked for premonitory urges and other sensory phenomena, disturbances of social behaviour, impulse control disorder, as well as for symptoms of depression or anxiety disorder. GTS was diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000), and only patients fulfilling DSM-IV criteria for GTS during the last year were included into the study. Lifetime history of symptoms indicative of GTS was assessed using the Diagnostic Confidence Index (DCI) (Robertson et al., 1999). The appropriate modules of the German version of the structured clinical interview for DSM-IV Axis I disorders (SCID-I) (Wittchen et al., 1997) was used to test for obsessive-compulsive disorder (OCD). Attention deficit hyperactivity disorder (ADHD) was diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000). Patients fulfilling criteria of OCD, ADHD or other co-morbidities were excluded from the study. Severity of tics was rated using the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989). Additionally, standardized video recording was performed and data were scored using the Modified Rush Videotape Rating Scale (MRVS) (Goetz et al., 1999), which provides a total tic impairment score ranging from 0 to 20 (Goetz et al., 1999). Moreover, the number of tics per minute during the video recording (performed without the examiner being in the room) was counted, as described previously (Orth et al., 2008). Two patients refused to be videotaped.

Image protocol

MRI was performed at 3 Tesla (Magnetom TRIO T1M, Siemens, Erlangen, Germany) with a gradient system providing a maximal gradient strength of 40 mT/m using an 8-channel head coil. The head was stabilized with foam pads to minimize head movements. Patients were instructed to suppress tics and minimize head movements during scanning as much as possible. DTI was performed using an echo planar imaging (EPI) sequence covering the whole brain (TE/TR = 105/18.500 ms, bandwidth = 1954 Hz/Px, 128 × 128 matrix, FOV 256 × 192 mm, 60 axial slices, 2 mm slice thickness without interslice gap, resulting in an isotropic voxel size of $2 \times 2 \times 2 mm^3$). Diffusion weighted images were sensitized for diffusion along 24 different directions with a b-value of 1000 s/mm². For every eight diffusion-weighted images, a non-diffusion weighted image (b=0 s/mm²) was acquired. Partial volume effects of CSF contaminates the quantification of diffusion parameters (Bhagat and Beaulieu, 2004; Chou et al., 2005), therefore we suppressed CSF signal by incorporating the fluid-attenuated inversion recovery (FLAIR) technique into our diffusion weighted imaging protocol. A section selective inversion radio-frequency pulse (TI = 2400 ms) was added before the excitation pulse. To increase signal-to-noise ratio, scanning was repeated twice, resulting in a scanning time of 16 min 59 s. Images were immediately inspected for movement artefacts, and scanning was repeated in case of visible artefacts. To increase signal-to-noise ratio, scanning was repeated twice, resulting in a scanning time of 16 min 59 s. Images were immediately inspected for movement artefacts, and scanning was repeated in case of visible movement artefacts. Structural imaging also included T1-weighted imaging of the whole brain using a Fast Low Angle Shot (FLASH) 3D sequence (TE/TR = 4.92/15 ms, flip angle 25°, 192 slices, 1 mm slice thickness, 20% gap, 256 × 256 matrix, FOV 256 × 256 mm).

Image analysis

Pre-processing

Diffusion weighted images were corrected for head motion and normalized to stereotactic anatomic space based on the Montreal Neurological Institute (MNI) coordinates. In a first step, the second to sixth $b=0$ images were aligned to the first $b=0$ image taking a least squares approach and a six parameter (rigid body) transformation using the diffusion toolbox implemented in SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). The realignment parameters of each $b=0$ image were applied to the following eight diffusion-weighted ($b=1000$) images, thus correcting for movements between each $b=0$ image. In a second step, the rotations performed during realignment of the diffusion-weighted images were applied to the gradient vectors, thus reorienting gradient directions accordingly. For each subject maximal translational (mm) and rotational (°) movements were derived from realignment parameters. Maximum translation and rotation were compared between patients and controls using a two-tailed Mann—Whitney U-test, which is a non-parametric test to evaluate whether the distribution of observations of ordinal measurements in two independent samples is equal (null hypothesis).

Motion corrected diffusion-weighted images were co-registered to a single-shot EPI volume acquired during the same session.
This single-shot EPI volume was spatially normalized to a standard MNI EPI template using SPM2. The resulting normalization parameters were then applied to the co-registered diffusion-weighted images. Eddy current correction was performed on the spatially normalized diffusion-weighted images using FMRIB’s Linear Image Registration Tool (FLIRT) from the FMRIB Software Library (FSL) (Jenkinson et al., 2002). Maps of FA, eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) and MD were generated using DTI Fit within the FMRIB’s Diffusion Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fdt/) (Smith et al., 2004). The resulting parameter maps were smoothed with an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. There is no gold standard for the choice of filter size in voxel-based morphometry (VBM) style analysis of DTI data, and filter size may influence the results of morphometric analysis (Jones et al., 2005). We chose a FWHM of four times the voxel-dimension of our diffusion-weighted images as this was previously reported to be appropriate for diffusion-weighted images (Jones et al., 2005).

**Statistical analyses: group comparison**

Individual maps of FA, $\lambda_1$, $\lambda_2$, $\lambda_3$ and MD were entered into a two-sample $t$-test for a voxel-based statistical comparison of regional diffusion characteristics between patients and controls. DTI is sensitive to changes in organization and integrity of the white matter, but DTI is of limited use to identify regional changes in cortical grey matter microstructure. Moreover, very low FA values are strongly affected by noise. Therefore, analysis was restricted to voxels with an FA value of $>0.15$. Since white matter usually has a regional FA of $>0.2$ (Beaulieu, 2002), we are confident that this cut-off included the entire white matter.

Significance level was set at $P<0.05$ and corrected for multiple comparisons using the False Discovery Rate (FDR) method with a cluster extent threshold of $\geq 10$ continuous voxels. For parameter maps with significant differences additionally voxels showing between-group differences of $P<0.001$ (uncorrected) are reported as trends. Probabilistic cytoarchitectonic maps implemented in SPM2 (Eickhoff et al., 2005) and a web-based Talairach atlas (http://www.neurovia.umn.edu/cgi-bin/tal_atlas) were used to verify the anatomical correlates of coordinates of interest. Clusters that showed significant FA differences between patients and controls served as volumes of interest (VOI) for further analysis.

**Probabilistic tractography**

Probabilistic tractography based on DTI was performed to characterize anatomical connectivity of areas with regional FA differences between groups using the FMRIB’s Diffusion Toolbox. To this end, clusters that showed significant FA differences between patients and controls served as seed areas for probabilistic tractography. Based on the calculated probability distributions of fibre orientations in each voxel, probabilistic diffusion tractography identifies the pathways that pass through a seed region and estimates the probability that these pathways pass through any other voxel in the brain (Behrens et al., 2003b). To generate probabilistic maps a total of 5000 individual streamlines were drawn for each seed voxel with a step length of 0.5 mm and a maximum step number of 2000. Curvature threshold was set at 0.2 (corresponding to a minimum angle of approximately $\pm 80^\circ$) to preclude implausible pathways and back-tracking of pathways. Fibre tracking was performed on individual data sets in original diffusion space. Individual seed regions as derived from group analysis were obtained by back-transformation of VOI from MNI space into individual anatomical space using the parameters derived from spatial normalization. The images resulting from probabilistic tractography provide for each voxel the probability of being reached by pathways starting from the seed region during 5000 streamlines drawn in each individual. To eliminate noise and outliers, we applied a threshold of 10% of streamlines as previously suggested (Ramnani et al., 2006). Individual results from tractography were then transferred back to MNI space to produce likelihood maps of fibre tracking for each subject. Normalized probability images were binarized, and these individual maps were used to generate a probabilistic tractography map at the group level. In these group probability maps each voxel is labelled with the number of patients or controls, in whom this voxel was reached by a pathway running through the seed region in $>10\%$ of samples. Statistical comparison of the individual probabilistic maps between patients and controls was performed by a permutation-based non-parametric two-tailed $t$-test using the FSL randomize tool with exhaustive testing and family-wise error correction for multiple comparisons (http://www.fmrib.ox.ac.uk/fsl/randomise/). Permutation testing involves arbitrarily exchanging labels (e.g. group allocation) of data points when performing significance tests. A reference distribution to which the statistical value of the hypothesis test is compared is obtained by calculating all possible values of the test statistic under the different allocations of data points and labels (Nichols and Holmes, 2002).

**Correlation with tic severity**

To address the clinical significance of altered diffusion parameters in GTS patients, tic scores (YGTTSS, MRVS, total tics per minute) were correlated with mean FA values in VOI as defined by between-group comparison using Spearman’s rank correlation (SPSS 13.0; www.spss.com). We used the Holm-Bonferroni method to adjust for multiple testing (Aickin and Gensler, 1996). In brief, this is an example of a closed test procedure, which performs more than one hypothesis test simultaneously. By this, it controls for the family wise error rate of all $k$ hypothesis at the given type I error rate $\alpha$, while each hypothesis is tested with the simple Bonferroni correction. This requires ordering the statistically tests by $P$-values in ascending order. First, the smallest $P$-value is compared to $\alpha/k$, and if it is less than $\alpha/k$, the null-hypothesis for this is rejected and the next $P$-value is looked at. The second $P$-value is compared to $\alpha/k-1$, the third $P$-value to $\alpha/k-2$, and this procedure is continued, as long as the null hypothesis can be rejected. If one of the hypotheses cannot be rejected, all hypotheses that have not been rejected at previous steps are accepted.

**Results**

**Clinical characteristics**

Clinical details of the study population are listed in Table 1. Mean disease duration was $26.5 \pm 8.5$ years. Mean DCI was $61 \pm 15$. At the time of assessment all patients had simple motor tics, while complex motor tics were present in $11/15$, simple vocal tics in $13/15$ and complex vocal tics in $4/15$. Mean YGTSS was $42 \pm 16$. All patients reported premonitory urges preceding at least some of their tics. Five patients were medication naïve, the others had been treated previously with different medications (tiapride, $n=8$; sulpiride, $n=4$; risperidone, $n=3$; aripiprazole, $n=1$; clonidine, $n=3$; haloperidol, $n=1$; olanzapine, $n=1$; pimozide, $n=3$; quetiapine, $n=1$). Six patients had stopped medication years before participation in the study. Only four patients had taken medication during the last year. Two of these had stopped medical treatment weeks (3 or 6 weeks, respectively) or months (3 or 6 months, respectively) prior to participation in the study.
Table 1  Clinical data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Age at onset</th>
<th>DCI (0–100)</th>
<th>YGSS (0–100)</th>
<th>Tics –overview</th>
<th>Tic count/min</th>
<th>MRVS total (0–20)</th>
<th>Tics - description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P01</td>
<td>33</td>
<td>M</td>
<td>12</td>
<td>63</td>
<td>46</td>
<td>mMvV</td>
<td>34</td>
<td>11</td>
<td>Blinking, eye movements, screwing up the eyes, facial grimacing, simple and complex head, shoulder, arm and leg movements, gestures, copropraxia, sounds, coughing</td>
</tr>
<tr>
<td>P02</td>
<td>23</td>
<td>M</td>
<td>6</td>
<td>61</td>
<td>57</td>
<td>mMv-</td>
<td>44</td>
<td>5</td>
<td>Blinking, eye movements, facial grimacing, simple and complex movements of nose, mouth, head shoulder and trunk, sniffing</td>
</tr>
<tr>
<td>P03</td>
<td>29</td>
<td>F</td>
<td>3</td>
<td>68</td>
<td>30</td>
<td>mMvV</td>
<td>Missing\textsuperscript{a}</td>
<td>Missing\textsuperscript{a}</td>
<td>Simple and complex eye and leg movements, throat clearing, muttering words</td>
</tr>
<tr>
<td>P04</td>
<td>27</td>
<td>M</td>
<td>7</td>
<td>68</td>
<td>31</td>
<td>mMv-</td>
<td>Missing\textsuperscript{a}</td>
<td>Missing\textsuperscript{a}</td>
<td>Blinking, simple and complex movements of nose and mouth, facial grimacing, simple leg movements, snorting</td>
</tr>
<tr>
<td>P05</td>
<td>22</td>
<td>M</td>
<td>10</td>
<td>47</td>
<td>26</td>
<td>mM-</td>
<td>27</td>
<td>8</td>
<td>Blinking, screwing up the eyes, simple and complex head, shoulder, arm movements, gestures</td>
</tr>
<tr>
<td>P06</td>
<td>39</td>
<td>M</td>
<td>12</td>
<td>100</td>
<td>77</td>
<td>mMvV</td>
<td>55</td>
<td>14</td>
<td>Series of simple and complex movements of eyes, face, shoulder, head, arm and leg, facial grimacing, gestures, copropraxia, coughing, throat clearing, coprolalia</td>
</tr>
<tr>
<td>P07</td>
<td>31</td>
<td>M</td>
<td>12</td>
<td>37</td>
<td>18</td>
<td>m- - -</td>
<td>9</td>
<td>4</td>
<td>Frowning, blinking, screwing up the eyes, simple leg movement</td>
</tr>
<tr>
<td>P08</td>
<td>54</td>
<td>M</td>
<td>13</td>
<td>57</td>
<td>49</td>
<td>mMv-</td>
<td>68</td>
<td>15</td>
<td>Blinking, facial grimacing, simple and complex head, shoulder, trunk and leg movements, coughing, throat clearing</td>
</tr>
<tr>
<td>P09</td>
<td>28</td>
<td>M</td>
<td>6</td>
<td>50</td>
<td>44</td>
<td>m-v-</td>
<td>36</td>
<td>9</td>
<td>Blinking, facial grimacing, frowning, simple head movements, coughing, throat clearing</td>
</tr>
<tr>
<td>P10</td>
<td>42</td>
<td>F</td>
<td>3</td>
<td>76</td>
<td>42</td>
<td>mMvV</td>
<td>63</td>
<td>13</td>
<td>Simple and complex neck and shoulder movements, simple leg movements, sounds, throat clearing, sneezing</td>
</tr>
<tr>
<td>P11</td>
<td>45</td>
<td>M</td>
<td>11</td>
<td>64</td>
<td>35</td>
<td>mMv-</td>
<td>63</td>
<td>10</td>
<td>Blinking, facial grimacing, trunk movements, gestures, coughing, throat clearing, sniffing</td>
</tr>
<tr>
<td>P12</td>
<td>29</td>
<td>M</td>
<td>3</td>
<td>54</td>
<td>36</td>
<td>mMv-</td>
<td>17</td>
<td>5</td>
<td>Facial grimacing, simple and complex movements of eyes, head, shoulder, hands and feet, gestures, noisy breathing</td>
</tr>
<tr>
<td>P13</td>
<td>34</td>
<td>M</td>
<td>6</td>
<td>52</td>
<td>56</td>
<td>m-v-</td>
<td>48</td>
<td>9</td>
<td>Blinking, facial grimacing, eye rolling and screwing up the eyes, simple shoulder and trunk movements, sounds</td>
</tr>
<tr>
<td>P14</td>
<td>38</td>
<td>M</td>
<td>11</td>
<td>45</td>
<td>22</td>
<td>m-v-</td>
<td>15</td>
<td>6</td>
<td>Blinking, grimacing, sniffing</td>
</tr>
<tr>
<td>P15</td>
<td>43</td>
<td>M</td>
<td>5</td>
<td>67</td>
<td>60</td>
<td>mMvV</td>
<td>65</td>
<td>11</td>
<td>Grimacing, simple and complex head, shoulder, trunk, arm and leg movements, series of multiple tics, snarling, coprolalia</td>
</tr>
<tr>
<td>Mean</td>
<td>34</td>
<td>8</td>
<td>61</td>
<td>42</td>
<td>42</td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Two patients refused to be videotaped.

M = male; F = female; Tics overview: m = simple motor; M = complex motor; v = simple vocal; V = complex vocal Tics; Tic count: tics per minute counted on video; MRVS (total) = total score of the Modified Rush Videotape Rating Scale.
Movement artefacts

No movement artefacts were noticeable by visual inspection. There was no difference in maximal translational or rotational movement between patients and controls (translation: median 1.1 versus 0.6 mm, \( P = 0.117 \); rotation: 1.0 versus 1.0°, \( P = 0.380 \); Mann–Whitney U-test).

Group differences in regional diffusion characteristics

In cerebral white matter FA reflects the degree of organization and integrity of white matter pathways. Patients with GTS showed a regional increase in FA in the white matter underlying the mesial part of the left central and postcentral gyrus compared with healthy controls (Fig. 1A, Table 2). Probabilistic cytoarchitectonic maps localized the maximum of the cluster to the white matter below Brodmann area (BA) 3a of the primary somatosensory cortex (S1) (Eickhoff et al., 2005). When lowering the threshold to an uncorrected \( P \)-value of 0.001, a bilateral trend to increases in regional FA became evident in the white matter below the postcentral (BA 3a) and precentral (BA 4p) cortex (Fig. 1B, Table 2). GTS patients showed additional trends towards a regional FA increase in the white matter below the left frontal medial gyrus (underlying the left supplementary motor area) and in the right ventral lateral thalamus (VL) and
ventral posterolateral thalamus (VPL). No cluster of a decrease in regional FA in GTS patients relative to healthy controls was identified, even at an uncorrected $P$-value of 0.001.

The third eigenvalue ($\lambda_3$) represents diffusivity perpendicular to the main diffusion direction. A single cluster of decreased $\lambda_3$ in GTS patients relative to healthy controls was identified below the mesial part of the left central sulcus and postcentral gyrus (Table 3). The location and extent of this cluster was largely congruent with the cluster showing a significant increase in FA. Lowering the threshold to an uncorrected $P$-value of 0.001 revealed a bilateral pattern of regional decreases in $\lambda_3$. Resembling the pattern of increased FA in GTS patients, regional $\lambda_3$ increases were located in the white matter below the pre- and postcentral gyrus bilaterally as well as in the right VL and VPL nuclei of the thalamus (Table 3). There were no areas of significant increases in $\lambda_3$ in GTS patients and no significant differences between patients and controls for $\lambda_1$, $\lambda_2$ or MD.

In the VOI defined by the area of increased FA in GTS patients the first eigenvalue was similar between groups, while patients showed lower MD, $\lambda_2$ and $\lambda_3$ than healthy controls (Fig. 2).

The increased regional FA in GTS patients were therefore caused by a reduced diffusivity perpendicular to the main diffusion direction (i.e. the main fibre direction) in this area, resulting in a more ‘cigar-shaped’ diffusion tensor and increased anisotropy of diffusion.

### Probabilistic tractography

Probabilistic tractography was used to assess which major pathways pass through the area of increased FA in GTS patients. Tractography identified ipsilateral pathways to adjacent primary somatosensory and motor cortices, connections to the ipsilateral VPL and further along the medial lemniscus stretching out to the superior cerebellar peduncle. Further pathways extended along the posterior part of the corpus callosum to the contralateral mesial sensorimotor cortex.

At a group level, probabilistic maps were very similar for patients and controls (Fig. 3). Furthermore, group comparison applying permutation non-parametric $t$-tests revealed no voxels showing significant differences in the probabilistic connectivity pattern between patients and controls. Three-dimensional visualization demonstrates the spatial distribution of ipsilateral and interhemispheric

### Table 2 Statistical results of group comparison—FA

<table>
<thead>
<tr>
<th>MNI peak coordinates (mm)</th>
<th>Cluster size (voxels)</th>
<th>P-values (voxel-level)</th>
<th>$T$</th>
<th>Anatomical allocation*</th>
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<td>$z$</td>
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*Anatomical allocation refers to the white matter below the named areas (except for the thalamus). PoCG = postcentral gyrus; PrCG = precentral gyrus; SLF = superior longitudinal fascicle; SMA = supplementary motor area; VL = ventral lateral thalamus.

### Table 3 Statistical results of group comparison—third eigenvalue ($\lambda_3$)

<table>
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<tr>
<th>MNI peak coordinates (mm)</th>
<th>Cluster size (voxels)</th>
<th>P-values (voxel-level)</th>
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<th>Anatomical allocation*</th>
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*Anatomical allocation refers to the white matter below the named areas (except for the thalamus). PoCG = postcentral gyrus; PrCG = precentral gyrus; SLF = superior longitudinal fascicle; SMA = supplementary motor area; VL = ventral lateral thalamus; VPL = ventral posterolateral thalamus.
connections of the volume of interest assignable to defined somatosensory and sensory-motor networks (Fig. 4).

**Correlation of FA with tic severity**

Individual mean FA values in the area showing increased FA in GTS patients were negatively correlated with total MRVS score ($R_s = -0.646$, $P = 0.017$) and total raw number of counted tics/minute ($R_s = -0.633$, $P = 0.020$) (Fig. 5), while there was no significant correlation with the YGTSS score ($R_s = -0.057$, $P = 0.840$). After adjustment for multiple testing using the Holm-Bonferroni method, correlations with total MRVS score and tic count/minute remained statistically significant with an overall type-I error rate $\alpha = 0.05$.

**Discussion**

Using DTI based morphometry we provide evidence for a structural alteration of somatosensory pathways in GTS. Patients with GTS showed a regional FA increase in subcortical white matter underneath the primary somatosensory cortex (BA 3a). Since these structural changes correlated negatively with tic severity, they might reflect a structural correlate of long-term adaptive reorganization in central sensory processing leading to improved tic control.

We used probabilistic fibre tracking to determine the major connectivity pattern of the region underneath the left somatosensory cortex. This region was mainly connected to thalamocortical and transcallosal cortico-cortical pathways that are crucial to somatosensory processing, involving the VPL and the medial lemniscus (Jones and Powell, 1970; Behrens et al., 2003a; Blatow et al., 2007). The tracked transcallosal cortico-cortical projections are known from primate studies (Iwamura, 2000) and passed through the posterior body of the corpus callosum where previous DTI studies have located transcallosal connections linking the primary somatosensory cortices of both hemispheres (Hofer and Frahm, 2006; Zarei et al., 2006). Additionally, the superior cerebellar peduncle was found to be connected to areas of altered FA.
in GTS patients. The superior cerebellar peduncle represents the major output of the cerebellum, including cerebello-thalamo-cortical pathways involved in sensory-motor integration (Hazrati and Parent, 1992). Altogether, these results indicate that the area of increased FA in GTS patients represents an important connectivity node of the somatosensory system. Furthermore, the results obtained with fibre tracking confirm that the observed between-group in regional FA differences do not follow from the

Figure 4 3D-visualization of pathways passing through the cluster of increased FA in GTS patients. 3D-rendering of voxels reached by probabilistic tractography in >10% of individual samples and >20% of all subjects (controls and GTS patients) is superimposed in green on the 3D-rendering of an individual T₁-weighted brain (generated by the fancy render function of the SPM2 volumes toolbox).

Figure 5 Correlation of FA with tic severity. Scatter plots of Spearman’s rank correlations of mean FA values in the volume of interest defined by the region of increased FA in GTS patients in the left mesial subcentral white matter with total MRVS score (left) and total number of tics/minute (right), including regression line and 95% CIs.
comparison of different fibre structures in the two groups, which might result from spatial shift, atrophy or a misalignment of diffusion-weighted images in patients, but by microstructural changes assignable to the tracked pathways.

DTI based morphometry revealed trends towards altered white matter organization in key areas of the somatosensory system beyond the primary somatosensory cortex. Regional FA was increased in the white matter below the precentral gyrus bilaterally, below the left SMA, and in the VL and VPL nuclei of the right thalamus. All these areas can be assigned to networks involved in sensory-motor processing. While the VPL is known to relay information from the spinothalamic tract and the medial lemniscus to the somatosensory cortex (Jones and Powell, 1970; Behrens et al., 2003a), the VL is an integral part of striato-thalamo-cortical and cerebello-thalamo-cortical circuits, with output to the primary motor and premotor cortex (Jones et al., 1979; Behrens et al., 2003a).

The identification of white matter abnormalities of somatosensory pathways in GTS is in good agreement with the concept of an involvement of the somatosensory system in the pathophysiology of GTS. Positive sensory phenomena represent a core clinical feature of GTS (Bliss, 1980; Kurlan et al., 1989; Cohen and Leckman, 1992; Scähil et al., 1995; Kwak et al., 2003). Premonitory sensations occur in over 90% of adult patients (Leckman et al., 1993) and can appear as localized itchies, tingling or burning, or as an increased sensitivity to tactile, auditory or visual stimuli (Cohen and Leckman, 1992; Leckman et al., 1993; Kwak et al., 2003). These urges might be the momentum driving the tic, and some authors have suggested that tics might represent a voluntary response to a premonitory sensory urge rather than a primary motor problem (Leckman et al., 1993; Kwak et al., 2003). Behavioural and neurophysiological studies provide further evidence of abnormal sensory-motor processing in GTS patients, showing abnormal grip force control (Nowak et al., 2005), disturbed postural control (Lemay et al., 2007), and reduced intracorticalafferent inhibition in a transcranial magnetic stimulation study targeting the primary motor hand area (Orth et al., 2005). Evidence of primary involvement of the sensorimotor cortex in the pathophysiology of GTS comes also from a recent structural MRI study, which demonstrated thinning of large parts of the sensorimotor cortex in children with GTS (Sowell et al., 2008).

Voxel-wise whole brain analysis of the other diffusion parameters only revealed a significant decrease of the third eigenvalue close to the area of most pronounced FA changes. However, a more detailed analysis of diffusion parameters in the volume of interest defined by the area of increased FA revealed significantly decreased mean values of MD, second and third eigenvalue, thus enabling us to attribute regional FA changes to a decreased diffusivity perpendicular to the main fibre direction in this area. This decrease of diffusivity might reflect an increase of barriers to diffusion or a loss of structures with fast diffusion perpendicular to the main fibre direction axis (Beaulieu, 2002). Possible anatomical explanations include more 'orderly' oriented axonal membranes or myelin sheaths parallel to the main fibre direction and less marked branching or crossing of fibres with a decrease of connections diverging from or crossing the main pathway direction (Beaulieu, 2002; Tuch et al., 2005; Hoeft et al., 2007). Similar findings of increased FA in defined white matter pathways associated with a pathologic condition have recently been reported for Williams syndrome (Hoeft et al., 2007) and Turner syndrome (Holzapfel et al., 2006) and been attributed to reduced branching or fibre crossing (Hoeft et al., 2007) or enhanced pathway development following excess use (Holzapfel et al., 2006).

Due to its cross-sectional character the present study cannot answer the question, whether increased FA in somatosensory connections is a long-term consequence of a primary sensory dysfunction in GTS or reflects compensatory structural changes. However, the negative correlation between regional FA in the left subcortical somatosensory white matter and tic severity provides a possible clue. The finding that more pronounced structural abnormalities were associated with fewer tics suggests that the observed FA changes represent a structural correlate of an adaptive mechanism within the somatosensory system. Previous morphometric MRI studies in GTS patients identified regional changes of grey matter volume in basal ganglia and cortical areas. Interestingly, the direction of these structural changes depended on the age of the patients suggesting a dynamic process (Peterson et al., 2001, 2007). Previous studies already demonstrated certain relations between structural brain alterations and tic severity in children and adults with GTS, contributing to the understanding of the nature of structural changes and their role in the course of the disease. For instance, patients with fewer tics showed regional increases in grey matter in prefrontal and parieto-occipital cortex (Peterson et al., 2001) as well as in the amygdala and hippocampus (Peterson et al., 2007), which was interpreted as a correlate of adaptive structural plasticity in areas engaged in inhibitory control leading to partial tic control. On the other hand, thinning of sensorimotor cortices was correlated with tic symptoms in children with GTS, suggesting that these brain regions play an important role in the pathogenesis of tics and GTS (Sowell et al., 2008). In the latter study most prominent findings were located in ventral parts of the motor and sensory cortex, a finding which the authors related to the prominent involvement of body parts represented in these areas (i.e. facial, oro-lingual and laryngeal musculature) in tics. Additionally, there was a negative correlation between facial tics and cortical thickness in these ventral sensory-motor areas, and between worst ever YGTSS and cortical thickness in more dorsal parts of the pre- and postcentral gyrus (Sowell et al., 2008). These findings cannot directly be compared with the results of the present study because we studied white matter changes rather than alterations of cortical thickness in adult GTS patients. However, one might speculate that whereas cortical thinning in GTS children related to tics might indicate primary abnormalities of brain maturation, our findings of white matter changes associated with better tic control in adult patients might represent adaptive plastic changes occurring at later stages of the disease. Reduced FA in the midsagittal corpus callosum of boys with GTS was also hypothesized to reflect neural plasticity decreasing interhemispheric connectivity resulting in better tic control via increased prefrontal activity (Plessen et al., 2006).
Given these considerations, the relative increase in regional FA within sensory pathways in GTS patients found in the present study might result from reduced fibre branching reflecting a reduction of horizontally organized cortico-cortical connections of somatosensory pathways. Reduced sensory-motor connectivity might help to reduce the spillover from an overactive sensory system to motor cortical areas, thereby attenuating the urge to move and reducing tic severity. Against the background of deficient sensory-motor integration in GTS patients (Nowak et al., 2005; Orth et al., 2005; Lemay et al., 2007), one might speculate that better tic suppression due to reduced sensory-to-motor connectivity may come at a price, resulting in a reduced capacity of sensory–motor interaction.

The analysis of possible associations of structural changes within the somatosensory system with sensory phenomena such as premonitory urges in GTS would also be of major interest. Currently, this is hampered by the lack of a widely used and validated scale for the assessment and quantification of premonitory urges in adults, although there is some experience with standardized assessment of urges in youths (Woods et al., 2005). In our sample all patients reported sensory phenomena preceding at least a proportion of tics. However, we did not further subdivide or quantify premonitory urges. Future studies are needed to systematically address this issue.

Of note, in GTS patients a regional FA increase was found in the white matter below the mesial somatosensory cortex. From studies in primates it is known that transcallosal connections between the somatosensory cortices are particularly dense in mesial parts where the trunk is represented. In contrast, interhemispheric connections are sparse in more lateral parts, i.e. representation areas of arms and hands (Killackey et al., 1983; Jones and Powell, 1969). In keeping with these data probabilistic fibre tracking identified strong transcallosal pathways connecting the mesial subcentral white matter to homologue areas in the present study. Increased FA as a reflection of altered fibre branching and organization may thus be particularly prominent in areas with strong inter-hemispheric connections. This is in line with findings of previous studies demonstrating altered inhibitory interhemispheric connectivity in GTS (Plessen et al., 2004, 2006).

Previous morphometric MRI studies performed region-of-interest based analyses of $T_1$- or $T_2$-weighted images. These studies revealed inconsistent results regarding cerebral white matter in GTS. The only DTI study reported until now looked at the mid-sagittal corpus callosum and found a reduced FA along the entire corpus callosum in boys with GTS (Plessen et al., 2006). Increased size of the corpus callosum was observed in children and adolescents with GTS (Baumgardner et al., 1996; Moriarty et al., 1997), while the corpus callosum was found to be decreased in adults (Peterson et al., 1994) and unchanged in girls with GTS in a different study (Motofsky et al., 1999). Frontal white matter was found to be both increased (Frederiksen et al., 2002) or decreased (Kates et al., 2002). We attribute these inconsistencies to the reduced sensitivity of conventional MRI morphometry to white matter changes, as well as to different methodological approaches used in the different studies. An additional cause for the discrepancies among previous morphometric MRI studies might be that heterogeneous groups of GTS patients were studied including children as well as adult patients, patients with significant co-morbidity, or patients taking neuroleptic medication (Peterson, 2001).

To overcome these limitations, we used DTI of the whole brain to specifically address morphometric changes of white matter changes in a group of currently unmedicated GTS patients without psychiatric co-morbidity. With this approach, we were not able to reproduce previous findings of regional structural white matter abnormalities in GTS patients. This might result from several reasons: most findings of white matter abnormalities in previous studies were reported in boys with GTS (Frederiksen et al., 2002; Kates et al., 2002; Plessen et al., 2006), while we studied adult GTS patients. Moreover, we studied a very selected patient population, characterized by the absence of psychiatric co-morbidity and the persistence of tics into adulthood, which is not the case in the majority of GTS patients (Robertson, 2000; Leckman et al., 2001). Therefore, the results of our study cannot be generalized to all GTS patients. This notwithstanding, we believe that the study of such a selected well-defined patient population represents a first step on the way to better delineate the neural basis of GTS. Another limitation of the present study is the small sample size. Results will have to be confirmed in independent and preferably larger samples of GTS patients. Finally, although none of the patients was taking neuroleptic medication at the time of MRI and most had stopped these drugs months to years before, we cannot fully exclude that previous neuroleptic medication influenced our results. Our study also differs from the above named studies in its methodological approach, using an observer-independent imaging analysis technique with voxel-based statistical analysis instead of user-dependent delineation of regional volumes. Finally, reduced sensitivity of DTI to changes in grey matter might explain why we did not find basal ganglia abnormalities, which were reported in several previous neuroimaging studies (Moriarty et al., 1997; Zimmerman et al., 2000; Peterson, 2001; Peterson et al., 2001; Bloch et al., 2005). While DTI is better suited to detect changes in white matter organization or integrity compared with $T_1$- or $T_2$-weighted MRI, it is less sensitive to structural changes in the cortical or subcortical grey matter. The thalamus is an exception to this because its tissue microstructure is similar to white matter resulting in higher FA values than in the cerebral cortex (Behrens et al., 2003a).

To summarize, using DTI we identified a specific increase of subcortical FA underneath the left primary somatosensory cortex which inversely correlated with tic severity in uncomplicated adult GTS patients. These structural alterations probably represent an adaptive response of the sensory–motor system to primary pathologic neural input or processing in GTS allowing for partial compensation of abnormal behaviour. Longitudinal DTI studies in affected children and adolescents are needed to better understand the dynamics of adaptive changes of brain structure in GTS.

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