Widespread affections of large fiber tracts in postoperative temporal lobe epilepsy

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ABSTRACT

Temporal lobe epilepsy with hippocampus sclerosis (HS) is the most frequent focal epilepsy and often refractory to anticonvulsant therapy. Secondary structural damage has been reported in several studies of temporal lobe epilepsy and unilateral hippocampal sclerosis. Applying diffusion tensor imaging (DTI) we investigated alterations in white matter following temporal lobe surgery in patients with medial temporal lobe epilepsy. We examined 40 patients who underwent surgery at our hospital for HS between 1996 and 2006 with diffusion tensor imaging (DTI). Images were obtained at a 3 T MRI scanner employing 60 gradient directions. Tract-based spatial statistics (TBSS), a novel voxel-based approach, was applied to analyze the data. Both patients with left- as well as right-sided surgery exhibited widespread degradation of fractional anisotropy (FA) in main fiber tracts not limited to the respective temporal lobe such as the uncinate fasciculus, the fronto-occipital fasciculus, the superior longitudinal fasciculus, the corpus callosum and the corticospinal tract on the respective hemisphere. Patients with left-hemispheric surgery showed more widespread affections ipsilaterally and also FA decrease in the contralateral inferior longitudinal fasciculus. DTI demonstrates widespread clusters of abnormal diffusivity and anisotropy in prominent white matter tracts linking mesial temporal lobe structures with other brain areas. Alterations in the ipsilateral mesial temporal lobe can be attributed to be a result of surgery, whereas extratemporal FA decrease is more likely the result of the underlying seizure disorder.

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Introduction

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) is one of the most common causes for drug refractory focal epileptic seizures (Engel, 1996). Usually the seizures start in early childhood and become pharmacologically intractable during the course of time (Engel, 2001). MTLE is also the most frequent indication for epilepsy surgery. Resection of the epileptogenic focus can significantly lower seizure frequency or result in seizure freedom in a majority of patients (Clusmann et al., 2002; Schulze-Bonhage, 2008; Wiebe et al., 2001). Widespread secondary structural damage even before surgery and not restricted to the primarily affected temporal lobe has been reported in several studies of unilateral MTLE with HS, ranging from temporolateral (Focke et al., 2008; Luat and Chugani, 2008) to frontal lobe involvement and including grey and white matter regions (Arfanakis et al., 2002; Bernasconi et al., 2004), as well as the corpus callosum (Pulsipher et al., 2007; Weber et al., 2007). However, the cause of these changes is unknown and different mechanisms are discussed, such as tissue edema, disturbances of the blood–brain-barrier, neuronal loss or axonal demyelinaisation. (Bernasconi et al., 1999; Margerison and Corsellis, 1966; Seidenberg et al., 2005; Sutula et al., 2003).

Diffusion tensor MRI (DTI) is widely used to characterize the white matter architecture of the human brain in vivo, providing information about integrity and organisation of fiber tracts. In particular, DTI has been applied as one promising technique for a parameterization of the brain’s white matter. Several scalar indices have been proposed to correlate with the underlying structure, fractional anisotropy (FA) being the one most commonly used to quantify the directionality of diffusion and thereby structural integrity of the tissue. It is highest in white matter tracts, significantly lower in grey matter and theoretically zero in cerebrospinal fluid, therefore allowing to differentiate between different types of brain matter (Le Bihan et al., 2001; Pierpaoli and Basser, 1996). Decreased FA values, indicating loss of white matter integrity, have previously been reported in the ipsilateral temporal lobe as well as in the cingulum, corpus callosum and external capsule in patients with MTLE both before and after surgery (Arfanakis et al., 2002; Concha et al., 2007; Focke et al., 2008; Gross et al., 2006). It is preferable to analyze changes of fractional anisotropy on a whole brain basis, to avoid a restriction to a priori defined brain

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region. Different voxel-based techniques for whole brain analysis of FA differences have been used extensively, voxel-based morphometry (VBM) being the most commonly used approach (Ashburner and Friston, 2000; Jones et al., 2005). This method usually requires smoothing and spatial normalization of images, (Focke et al., 2008; Smith et al., 2006), which is inappropriate for scalar values as fractional anisotropy. Tract-based spatial statistics (TBSS) is a novel VBM-like approach to register and analyze white matter changes in FA datasets, using exclusively non-linear registration techniques. The use of smoothing methods is not required, as FA values are projected on a skeleton of white matter tracts based on the individual subjects studied. It has been shown that this method increases the sensitivity and interpretability of white matter tract changes in neurological disease (Smith et al., 2006). Alternative approaches to analyze diffusivity changes on a whole brain basis are based on normal values (Deppe et al., 2007) or use automated tractography (Hagler et al., 2008).

We wanted to investigate white matter alterations and their correlation with the clinical outcome following temporal lobe surgery in patients with medial temporal lobe epilepsy applying high-resolution diffusion-weighted imaging.

Methods

Subjects

Forty-four patients who underwent epilepsy surgery due to intractable unilateral hippocampus sclerosis between 1996 and 2006 in our hospital were originally included into the study (m:22; mean age = 46.22 yrs). Four patients were examined but not included in the study due to problems with the MRI data acquisition (n = 1) or further brain surgery outside the medial temporal lobe (n = 3). Thus, 40 patients (male n = 20; female n = 20; mean age = 45.03 yrs, standard deviation 11.11 yrs) with either right (n = 21) or left-sided (n = 19) surgery were finally used for the analysis.

Prior to surgery all patients underwent our regular pre-surgical evaluation protocol including neuropsychological tests, structural MRI, interictal and/or ictal Video-EEG recording and in some cases WADA-Test, SPECT, fMRI or electrocorticography (Kral et al., 2002). The diagnosis of hippocampal sclerosis was confirmed by histopathological examination of excised tissue in all cases. Besides the imaging data, information about the current seizure frequency and present anticonvulsive medication were obtained. In all cases medical files concerning history and treatment of the individual patient were obtained from the archive and evaluated. For extensive clinical data see Table 1.

We also studied 28 age and gender-matched healthy controls (male n = 14; female n = 14; mean age = 43.43 yrs).

The ethics committee of the University of Bonn approved the study and all participants gave their written informed consent.

Imaging protocol

Magnetic Resonance Imaging was performed at the Life & Brain Center in Bonn on a 3 Tesla scanner (Magnetom Trio, Siemens, Erlangen, Germany). A neurovascular eight-channel head coil was used for signal reception. All subjects underwent the same imaging protocol consisting of whole brain T1-weighted, T2-weighted and diffusion-weighted structural imaging. The total study time was approximately 110 min per subject and all images were obtained in one session.

Diffusion-weighted data was obtained using an in-house DTI sequence. Images were acquired using single shot, dual echo, spin-echo echo planar imaging (EPI) (TR = 12 s, TE = 100 ms, 72 axial slices, resolution 1.72 × 1.72 × 1.7 mm, no cardiac gating). As parallel imaging scheme, a GRAPPA technique (acceleration factor 2.0) was chosen. Diffusion weighting was isotropically distributed along 60 directions (b-value = 1000 s/mm2). Additionally, seven data sets with no diffusion weighting (b0, b-value = 0 s/mm2) were acquired initially and interleaved after each block of 10 diffusion-weighted images as anatomical reference for motion correction. The high angular resolution of the diffusion weighting directions improves the robustness of probability density estimation by increasing the signal-to-noise ratio (SNR) and reducing directional bias. To further increase SNR, scanning was repeated three times for averaging, requiring a total scan time for the diffusion-weighted imaging protocol of approximately 45 min.

Directly after the DTI a 3D-T2-weighted dataset with 192 slices was obtained (RARE; TR = 2 s, TE = 355 ms, resolution 1.0 × 1.0 × 1.0 mm, flip angle 180°). T1-weighted images were obtained using an MP-RAGE sequence with 160 slices (TR = 1300 ms, TI = 650 ms, TE = 3.97 ms, resolution 1.0 × 1.0 × 1.0 mm, flip angle 10°).

Data analysis

All imaging data were transferred to a cluster of Linux workstations for processing. The structural images were visually inspected for any structural abnormalities by a board certified neurologist.

Preprocessing and analysis of diffusion data was done with an in-house protocol using FSL 4.02 tools (available at www.fmrib.ox.ac.uk/fsl). First the DICOM images were converted into a 4D NIfiti-File. Motion correction was then applied on all images using 7-parameter global rescale registration with a mutual information cost function and tri-linear interpolation as implemented in FLIRT (FMIRB Linear Image Registration Tool, Jenkinson and Smith, 2001). All baseline b0 images were aligned to a reference b0 image and the resulting linear transformation matrices were then applied to the diffusion-weighted images following each baseline b0 image. After correction for eddy-currents, the three repetitions were averaged to improve the signal-to-noise ratio. A binary mask differentiating between brain and skull structures was calculated for brain extraction using BET (Brain Extraction Tool, Smith, 2002) and applied to all images. Next fractional anisotropy (FA), mean diffusivity (MD), as well as the Eigenvalues of the diffusion tensor were generated using the DTIfit algorithm (Smith et al., 2004).

For voxel-wise analysis of FA we applied TBSS, that is also included in FSL (Smith et al., 2006; Smith et al., 2007). TBSS is a novel registration approach that has advantages over conventional VBM-like analysis of FA data with regard to partial volume effects and multiple comparison problems (Smith et al., 2006), leading to a higher sensitivity for identifying white matter changes (Focke et al., 2008). However, as TBSS is restricted to white matter tracts, changes of grey matter associated with epilepsy are not detected. First the FA maps were scaled with a factor of 10000 to achieve an approximate intensity range of 0 to 10000 as required by TBSS for the further processing steps. Afterwards all FA maps were aligned to the 1 × 1 × 1 mm MRIB58 standard space FA template using non-linear registration (Rueckert et al., 1999). By averaging of the individual FA maps a mean FA image was generated. A skeleton representing the major tracts was then derived from the FA maps and visually inspected, to determine a suitable threshold (a threshold of 2000 has been used). The final thresholded FA skeleton for each subject (contained in a 4D Nifti-image) was calculated and used to carry out voxel-based statistics. Group analysis was carried out using FSL randomise with 5000 permutations (Nichols and Holmes, 2002). It included group comparisons using 2-sample t-tests between the respective LHS/RHS groups and healthy controls and regression analysis with regard to clinical data (type of seizures, type of surgical approach, postoperative seizures, age at surgery, age at onset, time between surgery and MRI). The resulting statistical maps were family-wise error (FWE) corrected at the cluster level with a p-value of <0.05, thickened and superimposed on the mean FA image and the group...
Table 1
Clinical data.

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Seizure types: SPS = simple partial seizures; CPS = complex partial seizures; SGTC = secondary generalized tonic-clonic seizures.

Type of surgery: TLR = 2/3 Temporal lobe resection; SAH = selective amygdalohippocampectomy.

Current AED medication: LTG = lamotrigine; LEV = levetiracetam; CBZ = carbamazepine; OXC = oxcarbazepine.

Postoperative seizure status: 0 = none; 1 = early postoperative (<2 yrs, now none); 2 = late postoperative (>2 yrs, now none); 3 = now. All types of seizures including auras are used for classification.

Engel classification of current seizure status: Class I, seizure free or only auras since surgery; Class II, rare seizures (fewer than two/year or only nondisabling nocturnal seizures); Class III, reduction of seizure frequency more than 75%; Class IV, unchanged (<75% reduction of seizure frequency) (Engel, 1987 and 1993). AED = antiepileptic drug. (red.) = AED dose reduction.

skeleton as well as the MNI152 template supplied by FSL FSLview and its atlas tools (ICBM-DTI-81 white matter labels atlas; JHU white matter tractography atlas) as well as general neuroanatomical handbooks were used to allocate FA changes detected by TBSS to the different anatomical structures in the MNI152 space (Hua et al., 2008; Wakana et al., 2004).

Single masks for all affected structures in a group (LHS patients, LHS controls, RHS patients, RHS controls) were created and then used for extraction of mean FA values for every subject using FSLUTILS tools. These results were then transferred over to SPSS 17 (SPSS Inc., Chicago IL, USA) and mean FA values were then calculated for all affected white matter structures and every sub-group.

All FA images registered to the FA template using the TBSS algorithm were also processed with the VBM approach (Ashburner and Friston, 2000) used by SPMS (available at www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5 (The MathWorks, Natick, MA). For this the TBSS-generated 4-D-Nifti file containing all FA data was splitted into single files containing the subject's FA map. As these maps were already registered to the MNI152 space, further registration measures were not necessary. The files were then fed into SPM's VBM toolbox and group contrasts were defined. Using a general linear model a 2-sample t-test was carried out between controls and LHS/RHS groups respectively. Results were FWE corrected at p < 0.05 and superimposed on the MNI152 template brain. Clinical features were also used as covariates in further t-test statistic analyses. Furthermore regression analysis was initiated with regard to clinical data (see above).

To quantify the amount of surgical lesions, manual volumetry was applied. Two researchers manually identified the lesions on high-resolution T1-weighted images using FSLview. The created volumetry masks were transformed into MNI152 space using FLIRT. All masks in the respective groups (LHS/RHS) were then summed up to group specific masks with voxel-values ranging from 0 (no patient had surgery here) to 19/21 (tissue at this voxel was removed in all patients in this group). Furthermore the individual lesion volume (in ml) was calculated.

Clinical data was also analyzed with SPSS 17. The postoperative seizure outcome was evaluated using two different classifications. We used an in-house classification based on the time, when seizures occur postoperatively including all types of seizures including auras. Four different classes have been defined: 0 (no postoperative seizures at
all), 1 (seizures only in the first two years after surgery, now none), 2 (seizures more than two years postoperatively, now none) and 3 (ongoing seizures). Furthermore the classification introduced by Engel (1987, 1993) has been used. It focuses on the reduction of seizure activity postoperatively and also divides into 4 classes: Class I seizure free or only auras since surgery; Class II, rare seizures (fewer than two/year or only nondisabling nocturnal seizures); Class III, reduction of seizure frequency more than 75%; Class IV, unchanged (less than 75% reduction of seizure frequency).

Results
Clinical data

Of all patients included in the study, a majority was seizure free at the date of examination (75%, \(n = 30\)), with no significant difference between right- and left-sided surgery as well as type of resection or surgical procedure. Using the Engel classification, 33 patients were classified as Engel I (seizure free or only auras since surgery), 3 as Engel II (rare seizures), 2 as Engel III (more than 75% reduction in seizure frequency) and 2 as Engel IV (less than 75% reduction in seizure frequency). No correlation between the number of years after surgery and the postoperative seizure frequency was observed. 28 patients received anticonvulsive medication at a steady state level; two patients were on probatory dose reduction. Lesion volumes did not differ significantly between the two groups (12.945 ml in LHS vs. 10.546 in RHS, \(p = 0.093\)). For extent of lesions see Fig. 1. Correlations between lesion volume, outcome and altered diffusion parameters could not be observed.

For further clinical data see Table 1.

General analysis of FA values

Both patients with left- as well as right-sided surgery exhibit widespread degradation of fractional anisotropy (FA) in main fiber tracts not limited to the respective temporal lobe. However, changes in the group of patients with left-sided hippocampus sclerosis seem to be more extensive than with right-sided temporal lobe epilepsy. Both groups demonstrated bilateral FA changes, however these are slightly more extensive in the LHS group and different structures are affected
(Fig. 2). Results generated with SPM and TBSS were largely overlapping, the TBSS analysis however revealed a higher spatial concentration of the observed differences, which has also been reported previously (Focke et al., 2008; Smith et al., 2006). Due to this we only further discuss results produced by TBSS in this paper. Regression analysis with regard to clinical data (type of seizures, type of surgical approach, postoperative seizures, age at surgery, age at onset, time between surgery and MRI) calculated with both SPM and TBSS/Randomise showed no significant results. Detailed results are shown in Tables 2 and 3 and Figs. 2 and 3. Using a cluster based model and FWE correction, significant (p < 0.05) areas of FA increase could be detected in neither LHS nor RHS groups.

**DTI — left hippocampus sclerosis group**

Compared to control subjects TBSS analysis showed extensive reduction of FA in the ipsilateral hippocampus region and temporal lobe as an equivalent of the removed brain tissue. Besides these directly surgery related changes (see Fig. 1 for extent of surgery), widespread clusters of reduced FA were detected in ipsilateral major white matter tracts such as the corpus callosum (p = 0.001), cingulate gyrus (p = 0.0192), fasciculus uncinatus (p = 0.0002) and the corticospinal tract (p = 0.0024). Further changes were found in the superior longitudinal fasciculus (p = 0.0058), inferior longitudinal fasciculus (p = 0.0002) and inferior fronto-occipital fasciculus (p = 0.0006).

Contralateral changes of high significance were detected in the inferior longitudinal fasciculus (p = 0.0078).

The use of the surgical approach/resection extent (selective amygdalohippocampectomy (SAH) vs. 2/3 temporal lobe resection) as a covariate in the t-test showed a further area of FA reduction accordant to the inferior longitudinal fasciculus in patients that underwent 2/3 temporal lobe resection compared to selective amygdalohippocampectomy.

For FA- and p-values of all affected structures and further information see Table 2 and Figs. 2 and 3.

**DTI — right hippocampus sclerosis group**

In the ipsilateral hemisphere affected tracts included the fasciculus uncinatus (p = 0.0002), superior (p = 0.0068) and inferior (p = 0.0002) longitudinal fasciculus, anterior corpus callosum (p = 0.027), cingulate gyrus (p = 0.0214) and the corticospinal tract (p = 0.0038). We also observed an FA decrease in the ipsilateral anterior thalamic radiation (p = 0.0026). In the left hemisphere a significant FA decrease was only detected in the cingulate gyrus (p = 0.033).

**Table 3**

<table>
<thead>
<tr>
<th>Localisation</th>
<th>FA decrease in right-sided MTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral</td>
<td>FA patient group</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus/arcuate fasciculus</td>
<td>0.478</td>
</tr>
<tr>
<td>Cingulum</td>
<td>0.443</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>0.537</td>
</tr>
<tr>
<td>Fasciculus uncinatus</td>
<td>0.281</td>
</tr>
<tr>
<td>Anterior thalamic radiation</td>
<td>0.484</td>
</tr>
<tr>
<td>Fronto-occipital fasciculus</td>
<td>0.387</td>
</tr>
<tr>
<td>Inferior longitudinal fasciculus</td>
<td>0.464</td>
</tr>
<tr>
<td>Hippocampal part of cingulum</td>
<td>0.275</td>
</tr>
<tr>
<td>Corticospinal tract</td>
<td>0.593</td>
</tr>
<tr>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td>Posterior cingulum</td>
<td>0.532</td>
</tr>
</tbody>
</table>

For FA- and p-values of all affected structures and further information see Table 3 and Figs. 2 and 3.

**Discussion**

We showed widespread changes of diffusion parameters not restricted to the resected epileptogenic focus and the ipsilateral temporal lobe in patients with mesial temporal lobe epilepsy. Significantly lowered FA in the LHS/RHS patient groups compared to control subjects were detected in several important pathways in the ipsilateral temporal lobe, the limbic system and major tracts connecting to the medial temporal lobe. Changes seem to be generally more severe and extensive in patients with left-sided HS compared to right-sided HS, which has also been recognized previously (Focke et al., 2008).

As only postoperative DTI datasets were available for analysis, it is not possible to distinguish between changes of diffusion parameters due to the underlying disease and changes due to epilepsy surgery. We therefore used already published results of patients with HS to compare and interpret the white matter abnormalities detected in our study. To further test the differential effects of pre- and postoperative structural changes, longitudinal studies are necessary. However, the present study provides the largest sample of DTI data to the present day of medial temporal lobe epilepsy patients.

Ipsilateral FA decrease in the hippocampus region is the direct result of the surgical lesion, leaving a cyst filled with cerebrospinal fluid (CSF). The fractional anisotropy in these regions is approaching zero values, as diffusion in CSF is isotropic. Due to the TBSS approach of including only white matter tracts for analysis, these directly surgery related differences are not shown. However, FA-based VBM analysis done with SPM, covering both grey and white matter, revealed clusters of lowered FA values concordant with the lesion. As the hippocampus is a grey matter structure, the FA difference between intact tissue (in control subjects) and CSF (in the patient group) is less compared to white matter tracts vs. CSF. The extent of lesions is shown in Fig. 1.

As could be expected after brain surgery in this area, fiber tracts directly connected to the hippocampus undergo downstream Wallerian degeneration, for example the remaining posterior part of the parahippocampal gyrus, as the anterior part is removed in both SAH and temporal lobe resection. Being the major source of projections to the hippocampus but also the target of efferent hippocampal projections (Squire and Zola-Morgan, 1991), these direct degenerative processes affect especially the remaining parts of the parahippocampal gyrus. Connectivity between hippocampus and structures of the entorhinal cortex has been previously shown using DTI tractography (Powell et al., 2004). There have also been several voxel-based morphometry studies that investigated structural changes in
unilateral TLE, showing affections of the parahippocampal gyrus, entorhinal cortex and perirhinal cortex (Bernasconi et al., 2004; Keller and Roberts, 2008). In a quantitative tractography study (Yogarajah et al., 2008) affections of white matter connections of the parahippocampal gyrus were shown, with changes in LHS appearing more severe than in right-sided HS. This has also been reported in patients with TLE preoperatively (Focke et al., 2008). In our study, we found symmetric patterns of FA decrease in the posterior parahippocampal gyrus, with slightly more affected voxels in patients with LHS.

In both left- and right-sided HS we detected substantial FA reduction in the inferior longitudinal fasciculus (ILF), being a bidirectional connection between a number of temporal structures and functional areas and the occipital lobe (Schmahmann and Pandya, 2006). However in left HS the changes were more widespread, especially in the occipital part of the ILF and here we also observed a cluster of voxels with reduced FA in the contralateral ILF. As this degeneration affects the non-sclerotic temporal lobe, it may be a clue why memory deficits associated with left-sided TLE appear to be more severe, even though the entire function of the ILF is not yet fully understood. Using covariate analysis we could show, that the extent of ILF damage is dependent on the type of surgery, as in 2/3 temporal lobe resection (TLR) a larger part of the temporal lobe is being removed. Because of the low sample size of TLR in our sample, one has to be very careful to emphasize this result too much, though. Further investigations are needed to investigate the effect of different neurosurgical approaches on extratemporal white matter affections. The seizure outcomes of SAH and TLR are comparable, though patients after TLR suffer from more neuropsychological abnormalities (Clusmann et al., 2002).

We could also show a bilateral decrease of FA in the uncinate fasciculus (UF), which is linking the anterior temporal lobe with medial and orbital pre-frontal cortex areas in a bidirectional way (Schmahmann and Pandya, 2006). Decrease of the UF in the external capsule appears to be completely symmetric in both left- and right-sided TLE, however the FA decrease in the frontal part of the UF in LHS patients was significantly more extensive and reached into the white matter of the frontal pole. Verbal memory performance in patients with left- and right-sided HS differs already preoperatively, with a significant decline after left SAH (Gleiwsner et al., 2002). As the UF has an important role in the formation and retrieval of episodic memory (Squire and Zola-Morgan, 1991), the larger extent of changes in the UF in LHS might therefore result in the reduced verbal memory performance in LHS patients, as has been previously suggested by (Diehl et al., 2008).

The corpus callosum (CC) is the major interhemispheric commissure and plays a pivotal role in cognitive functions and seems especially prone to disturbances throughout cortical development. Affections of the corpus callosum in patients with TLE have been previously reported by our group, showing a decreased thickness in posterior callosal regions (Weber et al., 2007), as well as other DTI studies (Gross et al., 2006; Thivard et al., 2005). Here we detected alterations of diffusion parameters in the CC in both LHS and RHS patients compared to controls. Clusters of FA reduction were however located in different parts of the CC and of different size. To locate regions of FA decrease we used the segmentation proposed by Witelson (1989) and modified by Hofer and Frahm (2006). In RHS only a small portion of the ipsilateral anterior midbody of the CC (region II) shows affections by means of decreased FA values whereas in LHS affections of both genu (region I), midbody and isthmus/splenium (regions IV and V) parts of the CC could be detected. Furthermore, the number of affected voxels in LHS was considerably larger. According to both Witelson and Hofer fibers from regions IV and V connect to temporal lobe structures, even though not directly to the hippocampal formation. However, fibers of the dorsal hippocampal commissure, crossing the midline under the rostral portion of the splenium and the caudal part of the body of the CC, which would explain reduced FA values in these areas due to seizure activity (Gloor et al., 1993; Kim et al., 2008). This is concordant with findings in patients who did not undergo surgery and could possibly be a characteristic finding with TLE (Concha et al., 2007; Focke et al., 2008). The more anterior part of the CC with FA changes in the LHS group consists of commissural fibers connecting to prefrontal areas (Schmahmann and Pandya, 2006), the significance of this finding remains unclear at present.

Reduced diffusivity was also detected in the ipsilateral superior longitudinal fasciculus (SLF) in both RHS and LHS. The SLF is the largest fiber tract of the long association fiber system and connects the pre-frontal, parietal and temporal cortices (Catani et al., 2002). It has been reported, that FA reduction within this tract is related to verbal working memory performance (Karlsgodt et al., 2008). The damage to the ipsilateral SLF in left-sided TLE was significantly larger than in right-sided TLE. This is consistent with the different findings in neuropsychological studies, where patients with left-sided TLE show inferior performance in verbal memory tests both pre- and post-operatively compared to right-sided TLE (Gleiwsner et al., 2002). Unfortunately, contemporary neuropsychological data was not available for all patients and subjects in our study, so that no correlations with regard to neuropsychological scores could be calculated. It has been discussed, whether the SLF and the arcuate fasciculus (AF) should be seen as one and the same fiber tract or can be segmented into two parts. The latter can be assumed due to recent DTI-tractography study results (Schmahmann and Pandya, 2006;
processes, frequently impaired by TLE (Petrides, 1995; Schmahmann diffusivity in the caudal part of the CB are more likely in HS and TLE as the CB that is affected are not described. In our opinion, alterations of the lesion (RHS vs. controls and LHS vs. controls) and the exact part of induce changes of plasticity, interneuron loss and result in cognitive magnetic resonance studies suggest that repeated, brief seizures reported (Concha et al., 2007), unfortunately the impact of the side of with postoperative patients FA reductions ipsilateral to the HS were FA decrease can also be detected in the ipsilateral anterior and the contralateral posterior CB. This is an interesting finding, as (Focke et al., 2008) described FA reduction in pre-surgical patients bilaterally in the anterior cingulum in LHS and ipsilateral in RHS. In another study with postoperative patients FA reductions ipsilateral to the HS were reported (Concha et al., 2007), unfortunately the impact of the side of the lesion (RHS vs. controls and LHS vs. controls) and the exact part of the CB that is affected are not described. In our opinion, alterations of diffusivity in the caudal part of the CB are more likely in HS and TLE as this part contains direct connections to the hippocampus and parahippocampal gyrus and is therefore involved in working memory processes, frequently impaired by TLE (PETrides, 1995; Schmahmann et al., 2007).

Up to now, the exact mechanism of seizure-induced damage to the brain is unknown, even though experimental, neuropsychological and magnetic resonance studies suggest that repeated, brief seizures induce changes of plasticity, interneuron loss and result in cognitive impairment (Sutula et al., 2003). Fiber tracts originating from structures assumed to be epileptogenic (i.e. hippocampal formation and amygdala) and anatomical structures connected to these structures via WM-tracts have been referred to as preferential pathways of spreading electrical neuronal activity during seizures. These have been previously proposed by EEG and SPECT studies and include fornix, anterior thalamus, cingulum, parahippocampal gyrus, striatum, other basal ganglia and projections to the basal and lateral temporal neocortex (Mayanagi et al., 1996).

Conclusion
This is to our knowledge the first study using a white matter skeleton-based, voxel-based approach to assess white matter integrity in patients with temporal lobe epilepsy who underwent surgery. We could show that there are widespread clusters of abnormal diffusivity and anisotropy detectable in prominent white matter tracts linking mesial temporal lobe structures with other brain areas. Interestingly, fronto-temporal changes that are likely to be direct results of surgery appear to be nearly symmetric in LHS and RHS, whereas cluster-patterns of extratemporal degradation of fractional anisotropy differ significantly between the affected hemispheres. This underlines the assumption of different pathomechanisms and intensity between the affected hemispheres in TLE.

As only postoperative DTI data was available, we can only speculate on the direct surgical implications on white matter integrity. Comparing our results with preoperative data published by other groups (Concha et al., 2007; Focke et al., 2008; Hagler et al., 2008), the changes of fractional anisotropy detected postoperatively, seem to be more extensive which would be consistent with the assumption, that both epilepsy and surgery lead to neuronal loss and fiber tracts undergo Wallerian degeneration when disconnected from afferent and/or efferent structures. These degenerative changes are obvious in the symmetric fronto-temporal affections. Further, longitudinal studies are needed to disentangle the influence of the epilepsy and the surgery, respectively. Especially further analysis of pre- and postoperative data with regard to operation technique used, neuropsychological and functional imaging findings, outcome and type of seizures might help to understand how epilepsy damages the brain.

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References