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Changes in white matter microstructure in patients with TLE and hippocampal sclerosis

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ABSTRACT – *Objective*. Patients with mesial temporal lobe epilepsy (TLE) due to hippocampal sclerosis (HS) often show ictal and interictal propagation of epileptiform EEG activity to the ipsilateral temporal neocortex, the ipsilateral frontal lobe or the contralateral hippocampus, although structural MRI only shows unilateral involvement of the hippocampal formation. We used whole-head diffusion Tensor Imaging (DTI) to delineate a network that facilitates propagation of interictal epileptiform and seizure activity in this patient group. *Methods*. Isotropic 2 mm DTI was performed at 3 Tesla in 12 patients with medically intractable left TLE due to HS and compared to 12 controls. Whole-brain maps of fractional anisotropy (FA) were compared using a voxel based t-test to search for regions affected in patients with HS. This preliminary analysis was complementary to a set of anatomically guided region of interest (ROI) analyses that were manually defined on each individual's FA map. *Results*. Left HS patients showed FA decreases in the temporal lobe white matter bilaterally, the ipsilateral frontal lobe white matter (WM) and in the genu and trunk of the corpus callosum. ROI analysis identified a significant FA decrease in left HS subjects in the affected hippocampus, WM of the ipsilateral parahippocampal gyrus and the genu and trunk of the corpus callosum. *Conclusion*. WM alterations occur bilaterally in the temporal lobe and in the ipsilateral superior frontal gyrus in left HS. The etiology and significance of these changes are unclear but the role of these regions in epileptogenesis and for pathways of epileptic spread should be further investigated.

Key words: epilepsy, MRI, temporal lobe, seizure propagation, white matter microstructures, diffusion tensor imaging

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Epilepsy surgery is effective for the treatment of mesial temporal lobe epilepsy due to hippocampal sclerosis with about 60-86% of patients seizure-free one year after surgery (Wiebe *et al.*, 2001; Lowe *et al.*, 2004; Dupont *et al.*, 2006). One of the predictors of unfavourable post-surgical outcome is rapid interhemispheric propagation of seizure activity

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and even spread of interictal epileptiform activity to ipsilateral extratemporal areas or the contralateral hemisphere (Cascino *et al.*, 1995). Although seizure propagation patterns in patients with unilateral hippocampal sclerosis usually varies between and within patients, some common propagation patterns are described. Spread to the ipsilateral temporal neocortex or orbitofrontal cortex, the ipsilateral frontal lobe as well as to the contralateral frontal lobe and contralateral hippocampal formation are reported (Lieb *et al.*, 1991; Spencer *et al.*, 1987; Mueller *et al.*, 2004; Adam *et al.*, 1994), suggesting the existence of specific pathways for seizure propagation.

Previous imaging studies have shown abnormalities beyond the hippocampal sclerosis in HS-TLE suggesting a network extending outside the hippocampus and even beyond the ipsilateral temporal lobe. Thinning of the collateral white matter in the adjacent parahippocampal gyrus and atrophy of the ipsilateral mamillary bodies, fornix and thalamus have been reported (Keller *et al.*, 2002; Arfanakis *et al.*, 2002; Seidenberg *et al.*, 2005; Kim *et al.*, 1995; Moran *et al.*, 2001; Bernasconi *et al.*, 2004). Abnormalities of function previously reported include extrahippocampal changes of neocortical benzodiazepine receptor binding by PET or decreases in NAA/creatine and NAA/choline in the ipsilateral temporal lobe white matter by 1H MR spectroscopy (Hammers *et al.*, 2001; Sakamoto *et al.*, 2003).

More recently, diffusion tensor imaging (DTI) has been used to search for more widespread changes in white matter microstructure of individuals with HS. Using DTI, the white matter integrity has been assessed in a variety of clinical populations by examining a metric termed fractional anisotropy (FA) throughout the brain. FA is a measure of the directional bias of water diffusion which is to a large extent determined by the coherence of the underlying white matter. FA values are high in highly coherent large white matter tracts which result in highly anisotropic diffusion, such as the corpus callosum. FA is low in areas with a lower degree of organization or in areas of crossing white matter tracts where diffusion is more isotropic (Beaulieu, 2002; Basser and Jones, 2002). Regional differences in FA among populations indicate an alteration in the underlying WM tissue structure, yet the biophysical basis of FA alterations in pathology is an area of active study.

Previous studies using DTI in patients with unilateral HS have uncovered a number of important findings. Gross *et al.* studied seven patients with left TLE and four patients with right TLE using an axial fluid-attenuated inversion recovery (FLAIR) DTI-sequence and found significantly reduced FA in the genu of the corpus callosum and external capsule using an ROI-based approach (Gross *et al.*, 2006). Yu *et al.* (2006) investigated five patients with left and nine patients with right TLE due to unilateral HS and did not find any differences in FA in the hippocampus (HC) between patients and controls. However, other recent studies did demonstrate reductions in FA in the affected hippocampal formation (Salmenpera *et al.*, 2006; Kimiwada *et al.*, 2006; Assaf *et al.*, 2003) with additional extratemporal changes in the external capsule, the genu of the corpus callosum and the posterior part of the corpus callosum (Arfanakis *et al.*, 2002; Gross *et al.*, 2006). Whole brain FA analysis identified FA decreases in the ipsilateral temporal lobe and posterior extra-temporal regions but did not detect FA changes in the hippocampal or parahippocampal regions or the frontal lobes (Thivard *et al.*, 2005). However, this study used 5 mm slices which is likely to result in partial volume contamination, and combined left and right HS patients by inverting the right HS patients such that all abnormal hippocampi were on the left. Such procedures are not optimal because of inherent asymmetries in the human brain, and because this procedure would be confounded by conflating changes that could be unique to either population.

A number of differences in technical procedures could contribute to discrepancies with prior studies. The current study was aimed to utilize careful acquisition procedures that correct for confounding distortions in DTI data at higher resolution than reported in prior studies (reducing the confound of partial volume contamination) at 3 Tesla, providing the exquisite SNR needed for detecting microstructural alterations. Additionally, in contrast to prior studies which have only utilized ROI procedures, we employed complimentary ROI and whole brain analyses. The whole brain analyses provide rough estimate FA changes throughout the entire brain while ROI analyses of ROIs defined on the spatially normalized b = 0 volume provide a confirmation that the whole brain analyses were not affected by technical bias. We examined a well defined patient population with clear-cut left hippocampal sclerosis and compared these individuals to age- and sex-matched healthy controls. We performed complimentary whole brain statistical analysis and ROI-based analysis were performed to determine if bilateral temporal and frontal involvement could be confirmed.

Materials and methods

Subjects

Diffusion tensor images were obtained in twelve patients with left temporal lobe epilepsy (TLE) due to hippocampal sclerosis and 12 healthy patients, exactly age- and sex-matched controls *(table 1)*. All patients had clear-cut unilateral, left-sided hippocampal sclerosis with volume loss and a hyperintense signal in the left hippocampus on the FLAIR and the T2-weighted images. All underwent comprehensive presurgical evaluation in a tertiary epilepsy centre including video-EEG-monitoring. TLE was confirmed by EEG data showing unilateral left temporal seizure onset in all patients. All participants provided written informed consent. Participants were excluded if they had

Table 1. Characteristics of all patients included.

Pat#	sex	age	AO	Epilepsy	MRI	IOZ
1	m	52	16	TLE lt	HS lt	lt aTL
2	m	24	5	TLE lt	HS lt	lt aTL
3	m	32	0,3	TLE lt	HS lt	lt aTL
4	m	38	26	TLE lt	HS lt	lt aTL
5	f	29	5	TLE lt	HS lt	lt aTL
6	f	55	13	TLE lt	HS lt	lt aTL
7	m	54	36	TLE lt	HS lt	lt aTL
8	f	42	14	TLE lt	HS lt	lt aTL
9	f	32	16	TLE lt	HS lt	lt aTL
10	f	54	34	TLE lt	HS lt	lt aTL
11	f	41	16	TLE lt	HS lt	lt aTL
12	m	27	21	TLE lt	HS lt	lt aTL

AO: age at onset; MRI: MRI diagnosis; IOZ: ictal onset zone; TLE: temporal lobe epilepsy; lt: left; HS: hippocampal sclerosis; aTL: anterior temporal lobe (electrode Sp1 or T4).

a history of other neurological or psychiatric disorder. All participants received a high-resolution whole-head DTI scan (Siemens, Erlangen Germany, 3 Tesla Trio System; TR = 24, TE = 81, slice thickness = 2 mm, 60 slices total, FOV 128 x 128 mm for 2 mm isotropic voxels, six averages, six noncolinear directions with a b value = 700 s/mm^2 and one low-b image with a b value = 0 s/mm^2, aquired axially along the ac/pc-line). This scan was developed to optimally reduce eddy current distortions using a twice-refocused balanced echo (Reese *et al.*, 2003). Head motion was minimized by the use of tightly padded clamps attached to the head coil.

Image analysis

All data processing was performed using tools available as part of the Freesurfer (http://surfer.nmr.mgh.harvard.edu), and FSL (http://www.fmrib.ox.ac.uk/fsl) processing streams. DTI data were processed using a multistep procedure to achieve motion and residual eddy current distortion correction. The corrected volumes were used for the calculation of the fractional anisotropy maps as described previously (Salat *et al.*, 2005).

Whole brain maps

A spatial transformation of each participant's low-b volume to a low-b template in MNI/Talairach space was performed to allow group comparison. The FA data were resampled using the transformation created as before. A voxel-based calculation of group statistics on the spatially normalized data was performed. Each of these steps is described in detail elsewhere (Salat *et al.*, 2005).

Regional analyses

All ROIs were defined on the spatially normalized b = 0 volume of each individual participant using Tkmedit in the Freesurfer data processing package. The b = 0 volume is acquired with similar imaging parameters as the volumes with directional diffusion information but no diffusion gradients are applied, resulting in an anatomical echo planar T2 weighted volume in full registration with the dependent variable FA volume. Thus, the use of the b = 0 volume allows for the placement of ROIs without the influence of the dependent variable (FA) or use of a differentially distorted scan acquisition. Five hemispheric regions of interest (ROI) were placed bilaterally in addition to ROIs placed in the genu, trunk and splenium of the corpus callosum and in the affected and non-affected hippocampus. We selected regions which mainly contained white matter such as the corpus callosum, deep white matter of the frontal lobe and the temporal lobe and selected the parahippocampal gyrus as a special region of interest.

All ROIs were placed using a standardized placement procedure utilizing predefined atlas-based rules with morphological landmarks in each individual participant's b = 0 volumes. All ROIs were placed on the b = 0 image by the same rater, who was blinded to participants group, age and sex, and were created as a sphere with a diameter of 4mm (totaling 33 1 mm^3 isotropic voxels) to avoid arbitrary sizes of ROIs across participants, and to avoid inclusion of multiple white matter bundles in regional measurements.

Statistical analyses

Whole brain maps

Exploratory whole-brain analysis was performed using a voxel-based statistical comparison. Spatially normalized FA maps were compared by regression analysis (with duration of the disease in years, seizure frequency, frequency of interictal epileptiform activity, number of anticonvulsive drugs and handedness and regressed as a continuous variable across each voxel in the volume) and by voxel based t-test across the two groups.

Region of interest analysis

Data were analysed restricting the ROI inclusion to be limited to voxels with an FA value greater than 0.15, essentially masking out CSF and restricting the data to brain tissue only. ROI data were examined by t-test between groups. Statistical p-values of < 0.01 were considered statistically significant.

Results

Whole brain analysis

Results of the voxel-based t-test analysis are presented in *figure 1*. These analyses demonstrated several regions with significantly decreased FA in the patient group com-

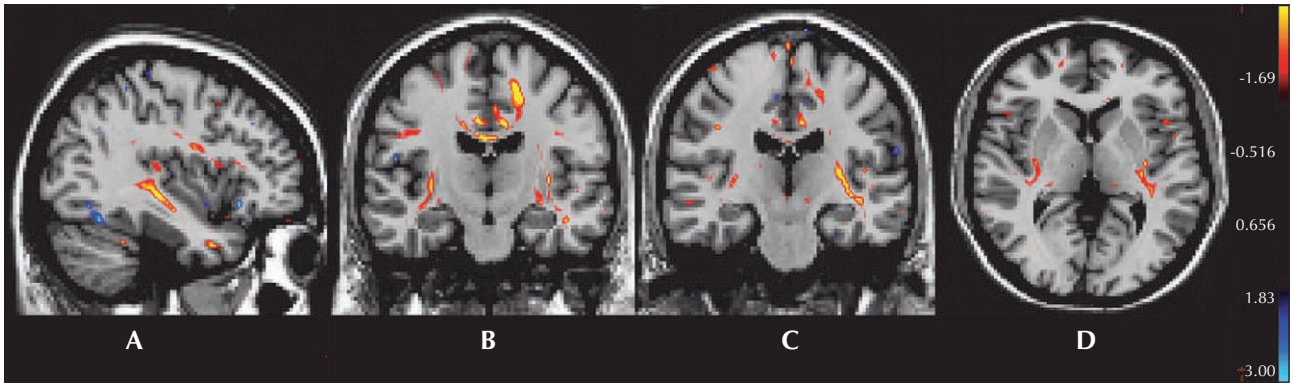

Figure 1. Map of the main FA decrease in patients with HS-TLE compared to healthy, age- and sex-matched controls. Volume maps of FA decline with disease computed by voxel level t-tests between the patients and the controls. Significant decline of FA ($p < 0,05$) was displayed in red/yellow. The colour scale at the bottom represents the significance of the FA change with yellow indicating regions of most significant decline. **A**) Sagittal view of the left temporal lobe showing decreased FA in the temporal lobe white matter. **B**, **C**) Coronal views showing the reduced FA bitemporally, in the left frontal region and in the corpus callosum. **D**) Axial view showing reduced FA in the temporal white matter.

pared with controls, including the temporal lobe white matter bilaterally, genu and trunk of the corpus callosum and the ipsilateral left frontal white matter. Linear regression was calculated voxel by voxel against the duration of epilepsy and spike and seizure frequency, the number of anticonvulsive drugs and handedness did not show any significantly related voxels ($R^2 < 0.3$).

Regional analyses

Preselected, manually placed ROIs were used to compare the findings from the whole-brain maps. Analysis confirmed the reductions of FA in the genu and trunk of the corpus callosum in patients compared to controls. In an intra-individual comparison, the affected hippocampus showed a significantly decreased FA compared to the healthy side *(table 2, figure 2)*. There was regional variability in FA values. As expected, WM regions with homogeneous orientation such as the corpus callosum had relatively high FA values, and more superficial and less coherent regions such as the subcortical frontal WM had relatively lower values of FA. Overall, the FA was reduced in all ROIs in patients compared to healthy controls but these reductions only reached significance in the corpus callosum as well as the ipsilateral parahippocampal gyrus *(table 2, figure 3)*.

Discussion

The current study demonstrates widespread, but regionally selective disease-related alterations in brain white matter organization measured by diffusion anisotropy. Whole head FA comparisons show that microstructural brain changes were most notable in the ipsilateral frontal lobe, the parahippocampal region and in both temporal lobes. This finding suggests that the structural brain changes in TLE due to HS extend far beyond the affected temporal lobe. These findings support the speculation that specific and probably functionally relevant fibre tracts are affected in HS-TLE that might enable propagation of seizure activity and interictal epileptiform activity. In our study, both temporal lobes seemed to be affected, possibly following the hippocampal commissure (Spencer *et al.*, 1987), as well as the ipsilateral frontal lobe, possibly following the uncinate fascicle (Ebeling and von Cramon, 1992).

Regional analysis showed significantly decreased FA values in the affected hippocampus compared to the healthy side. Significantly lower FA values were found in the in the genu and trunk of the corpus callosum. Although decreases in FA were found in all ROIs, none of the other differences were significant. Thus the ROI analysis confirmed a reduced FA in the genu of the corpus callosum. However, using ROI analysis we did not find significant changes in the other regions such as the middle and posterior corpus callosum, the superior frontal gyrus and the frontal white matter or the inferior frontal gyrus, although the whole-brain maps suggested a widespread affection of the frontal lobes. These differences point out the strengths and weakness and therefore complimentary nature of these two approaches. Whole-brain analysis can pick up confluent areas of unsuspected change but is insensitive to small focal changes. ROI analysis on the other hand requires predefined areas of interrogation and can detect small areas of involvement, but cannot define the extent of change and may be unable to identify regions of significant change if the ROI is not placed precisely in the altered area.

Previous studies have found decreased FA in the posterior extratemporal regions (Thivard *et al.*, 2005) and in the posterior part of the corpus callosum that could not be confirmed in our study. This might be due to methodical discrepancies between our studies. Different voxel sizes

Table 2. FA values of ROIs (including standard deviation) of TLE patients and controls. FA values were consistently low in patients. Significant FA-changes ($p > 0.05$), marked with *, occurred in the anterior, middle and posterior part of the corpus callosum and in the left parahippocampal gyrus. Data was analysed using an unpaired 2-sided t-test.

Region of interest (ROI)	FA controls	SD Controls	FA TLE lt	SD TLE lt	p
Anterior corpus callosum*	0,75191	0,0169777	0,6607	0,0233445	0.002
Middle corpus callosum*	0,591125	0,0145158	0,527108	0,0155632	0.008
Posterior corpus callosum*	0,85976	0,020956	0,80929	0,019013	0.029
Left superior frontal gyrus	0,405985	0,0154339	0,381958	0,0213707	0.525
Right superior frontal gyrus	0,39432	0,0135863	0,375958	0,0302305	0.099
Left frontal white matter	0,31036	0,0096845	0,291083	0,0190387	0.255
Right frontal white matter	0,326415	0,0116058	0,3108	0,0135141	0.209
Left inferior frontal gyrus	0,400589	0,0202271	0,381664	0,0306892	0.832
Right inferior frontal gyrus	0,409975	0,02136	0,379836	0,0242143	0.145
Left temporal lobe white matter	0,399732	0,0445683	0,375373	0,0213409	0.553
Right temporal lobe white matter	0,327342	0,0154021	0,313118	0,0171103	0.582
Left parahippocampal gyrus*	0,384594	0,0111314	0,34068	0,0270088	0.021
Right parahippocampal gyrus	0,402	0,0192854	0,360509	0,0233395	0.061
Left Hippocampus			0,35365	0,0751614	
Right hippocampus			0,42669	0,056315	

may well explain the different amount of anatomical structures included in each voxel: smaller voxel sizes allow us to detect more subtle changes in anatomical subregions and to even include not only regions of central white matter but also regions close to CSF or cortex.

Relation to prior imaging and histological data

The present data are in agreement with prior volumetric imaging studies demonstrating bilateral atrophy of the thalamus, lenticular nuclei, cerebellum, ipsilateral entorhinal cortex, perirhinal cortex, fusiform gyrus and frontal lobes (Keller *et al.*, 2004; Szabo *et al.*, 2005; Seidenberg *et al.*, 2005). Similarly, these data are in agreement with prior DTI studies using an ROI-based approach showing reductions in FA in the corpus callosum (Gross *et al.*, 2006; Arfanakis *et al.*, 2002) and middle frontal gyrus bilaterally (Flugel *et al.*, 2006). This suggests that microstructural changes measured by DTI do not occur randomly but seem to follow specific anatomical pathways. One of the main fibre bundles connecting the anterior temporal lobe with the middle frontal lobes *via* the corpus callosum is the uncinate fascicle (Highley *et al.*, 2002). Data suggests that the FA changes might occur along this anatomical pathway. Commissural fibres connecting both temporal lobes are the hippocampal commissure and the commisura hippocampi. The current data support a selective vulnerability of these particular fibre bundles, with a relative sparing of other tracts and areas, especially the posterior WM regions in the brain.

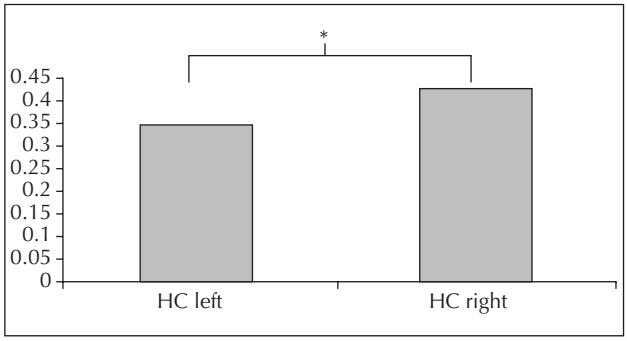

Figure 2. Regional differences in FA in the hippocampus of patients with left HS-TLE compared to healthy controls: The FA measured in the affected hippocampus was significantly reduced compared to the healthy side.

Still, the true nature of the tissue alterations underlying changes in FA is currently unknown, and important developing applications of MR techniques such as DTI will further histopathologically characterize regional changes measured *in vivo*. In future, DTI might be used to demonstrate pathways of epileptic spread or eloquent tracts and may change our concept of epilepsy surgery.

Diffusion anisotropy measures provide a metric of tissue characteristics that could ultimately represent a microstructural basis of volumetric measurements. Thus, these techniques represent a potential link between the MR and histological domains. However, DTI studies have some limitations. First, although a balanced echo sequence was employed to reduce eddy current distortion, and post processing was used to reduce residual distortion and motion, echoplanar scans are susceptible to additional distortions including reduced signal in susceptibility regions of the brain. Analyses were limited to regions

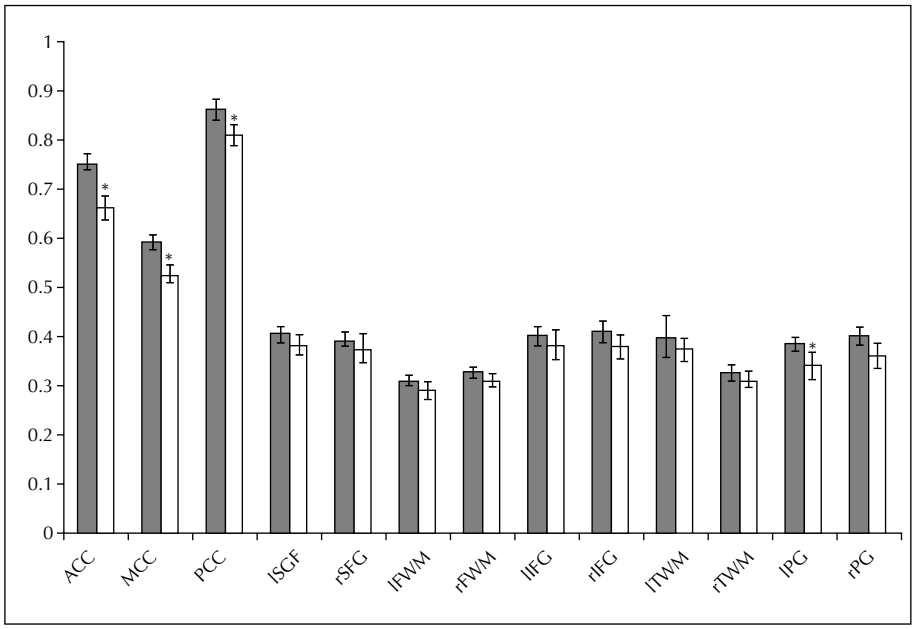

Figure 3. Regional FA values in patients with left temporal epilepsy due to hippocampal sclerosis and in healthy controls.
* Significance; ACC: anterior corpus callosum; MCC: middle corpus callosum; PCC: posterior corpus callosum; SFG: superior frontal gyrus; FWM: frontal white matter; IFG: inferior frontal gyrus; TWM: temporal lobe white matter; PG: parahippocampal gyrus; r: right; l: left.

of deep WM in an attempt to avoid this limitation. Still, development of DTI sequences using non-echo planar techniques would be useful for addressing this potential drawback. Additionally, such sequences would be useful for more accurate spatial transformation of DTI volumes across participants for whole-brain group maps. The regional measurements are limited since they only sample a small portion of the entire region. We therefore performed a whole-head comparison providing non-biased automated analysis of all brain regions.

Taken together, the current study demonstrates regional vulnerability and regional preservation of brain WM in patients with temporal lobe epilepsy. Further studies that correlate these findings with neuropsychological testing as well as validation with histopathological results are needed to further validate and understand the implications of these findings. □

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