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Research article

Bilateral cingulum fiber reductions in temporal lobe epilepsy with unilateral hippocampal sclerosis

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ABSTRACT

Purpose: To evaluate whether white matter tracts within the Papez circuit are altered in patients with unilateral hippocampal sclerosis (HS).

Methods: Twenty patients with histologically proven unilateral HS and 20 age-matched controls were studied with a 3 T Epilepsy-dedicated MRI protocol including a MPRAGE sequence for hippocampus volumetry and a diffusion tensor imaging (DTI) sequence (61 diffusion-encoding directions, 2 × 2 × 2 mm^3 voxels) for diffusion tensor tractography (DTT). An energy-based global tracking algorithm was used to calculate streamline counts (SC) and fractional anisotropy (FA) of cingulate, fornix, and mammillo-thalamic tracts, respectively.

Results: Sclerotic hippocampi were significantly smaller compared to the contralateral side and to age-matched controls. Cingulum SC but not FA were reduced on the hippocampal sclerosis (258 + 81.0) and contralateral side (271 + 85.6) compared to age-matched controls (447 + 138).

Conclusion: Focusing on white matter tracts of the Papez circuit we showed that in patients with intractable temporal lobe epilepsy unilateral hippocampal sclerosis is associated with a bilateral reduction of cingulum association fibers projecting from the cingulate gyrus to the parahippocampal gyrus.

Hippocampal sclerosis (HS) is a frequent cause of mesial temporal lobe epilepsy (mTLE) and histologically characterized by marked cell loss in the hippocampal CA1, less intense loss in the CA3/4 and relative sparing of CA2 regions. A CA1 predominant cell loss is found in 11% and a CA4 predominant cell loss in another seven% of patients [1]. While the latter may be missed, classical and CA1 predominant HS is reliably identified with Epilepsy-dedicated MRI protocols [2]. Although HS is often the only obvious lesion, additional structural abnormalities such as mammillary body, fornix, temporal lobe atrophy, and anterior temporal lobe gray white matter demarcation loss, and hemispheric atrophy may exist [3–6]. Voxel-based morphometry (VBM) in patients with mesial TLE shows additional atrophy of putamen, pallidum, middle and inferior temporal gyri, amygdala, and ceberellar hemispheres [7].

Extratemporal structural abnormalities suggest to consider HS as network disease with widespread gray and white matter alterations in which either more extensive initial damage has happened or secondary degeneration due to excicotoxic ictal epileptic discharges occurs.

The hippocampal formation is part of the Papez circuit [8]. Within this circuit, the cingulum forms an external ring interconnecting the cingulate cortex with the parahippocampal gyrus. The fornix forms an internal ring interconnecting the hippocampus with the mammillary bodies. The mammillary bodies are connected via the mammillo-thalamic tract to the anterior nucleus of the thalamus and from there via a thalamo-cortical tract to the cingulate gyrus [9,10]. The anterior parahippocampal gyrus (entorhinal cortex) receives inputs from the cingulum and is the major input to the hippocampus, the fornix the major output.

Aim of this study was to evaluate whether white matter tracts within the Papez circuit are altered in patients with unilateral HS. Diffusion measures of these white matter tracts were calculated with an energy-based Global Tracking algorithm [11,12].

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1. Patients and methods

1.1. Patients

Twenty patients (10 male, mean age 41.5 + 14.4 years) with histologically proven HS (10 left-sided, 10 right-sided) and 20 age-matched controls (45.9 + 16.7 years) were included. Patients were recruited from the Epilepsy Centers Freiburg and Kork, Germany between 2012 and 2016.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the local ethics committee of the University of Freiburg (EK-Freiburg: 215/13). All patients gave informed consent.

Unilateral TLE diagnosis was based on clinical history, seizure semiology and Video-EEG monitoring [13]. All patients had interictal- and ictal EEG recordings concordant to unilateral HS as the only epileptogenic MRI lesion.

1.2. MRI

MRI was performed on 3 T scanners (Magnetom TIM Trio, Magnetom Prisma, Siemens Medical Solutions, Erlangen, Germany) with 32 or 40 channel head coils and Epilepsy-dedicated protocols including the following key sequences [14,15]:

3D-T1-weighted MPRAGE (sagittal orientation, 160 slices, 1 × 1 × 1 mm, TI, 1100 ms; TR, 2200 ms; TE, 2.15 ms; Flip angle, 12°; 7:04 min)

3D-FLAIR-SPACE (sagittal orientation, 160 slices, 1 × 1 × 1 mm, TI, 1800 ms; TR 5000 ms; TE 388 ms variable; 6:42 min)

T2-STIR (coronal orientation, 40 slices, 0.45 × 0.45 × 2 mm, TI, 100 ms; TR 5300 ms; TE 24 ms; Flip angle 140°, 7:59 min)

For DTI, a single-shot spin EPI sequence was acquired on a different day (axial orientation, 69 slices, 2 × 2 × 2 mm^3, TR, 10.5 s; TE, 96 ms; 61 diffusion-encoding directions; b-value, 1000 s/mm^2;12-channel head coil, 11:40 min). Deformation correction was performed according to Zaitsev et al. [16].

1.3. Visual evaluation

MRI scans were independently analyzed by two neuroradiologists with more than 15 years experience (HU, KE). HS was diagnosed when hippocampal atrophy and/or an increased signal on FLAIR and/or T2 weighted images were visible. Structural abnormalities such as mammillary body atrophy, fornix atrophy, anterior temporal lobe gray white matter demarcation loss were noted, and diverging assessments solved in a consensus reading [6].

1.4. Hippocampal volumetry

Hippocampal segmentation was performed with FreeSurfer (v 5.3.0) (http://surfer.nmr.mgh.harvard.edu/) based on the MPRAGE sequences [17]. The volume is linear registered to MNI305 after B1 bias field correction and intensity normalization. Based on intensity and neighbor constraints, voxels are classified as white matter or other brain tissues. The boundary between the white and gray matter and between the gray matter and CSF is detected by following the intensity gradient. After high dimensional nonlinear registration to MNI305 atlas, brain is segmented into 45 regions (putamen, hippocampus, ventricles, et al.) based on atlas and measured values, here the volumes of both hippocampi were registered.

1.5. DTT

DTI data were processed using a MATLAB-based in-house toolbox for fiber tracking (http://www.uniklinik-freiburg.de/mr-en/research groups/diffperf/fibertools.html). After correction for motion and distortion artifacts [16] whole brain streamline reconstruction was performed using an energy-based global tracking algorithm.

Parameters were a cylinder width of 1 mm and a cylinder length of 3 mm. The weight of a cylinder segment was set to one-fourth of the brain-averaged anisotropic signal component, resulting in a “dense” reconstruction with an average of 30 cylinders per voxel. (11). Note that cylinder segments should not be imagined as hard cylinders, but as fuzzy objects that can intersect such that their superposition explain the observed diffusion signal. The weight parameter is comparable to a FA threshold: For higher weights, SC are reduced and a significant amount of streamlines is only revealed for regions with highly anisotropic diffusion distribution. Conversely, a lower weight leads to high SC, even in regions with a low FA. Given the low weight selected here, the number of iterations was set to 3×10^8. Finally, the temperature schedule for the cooling phase of the polymerization process was chosen exponentially with a starting temperature of 0.1 to a stop temperature of 0.001 [11].

The following white matter tracts were reconstructed: cingulum, fornix, mammillo-thalamic tract. In order to separate them inclusion and exclusions ROIs were placed on color-coded DT images, in which a red color indicates a preferential diffusion direction along the x, a green color along the y, and a blue color along the z axis, respectively.

To select cingulum streamlines, a spherical ROI was placed in a coronal color-coded DT image approximately 15 mm posterior to the anterior commissure selecting all green colored voxels within the cingulum (Fig. 1A). A midsagittal plane was used to exclude fibers from the opposite cingulum (Fig. 1C)

To select fornix fibers a ROI was placed in a coronal color-coded DT image approximately 10 mm posterior to the anterior commissure in which fornix streamlines appear green. Additional ROIs were placed on the fornix where it separates into the crura and in the hippocampal region.

To select mammillo-thalamic tract streamlines, a ROI was placed in axial color-coded DT images including blue color coded voxels laterally adjacent to the 3rd ventricle, superior to the mammillary bodies and some millimeters posterior to the fornix streamlines including only blue color coded voxels.

Finally, within these areas of white matter tracts SC and FA mean values were calculated.

1.6. Statistics

Hippocampal volumes, SC and FA of cingulum, fornix, and mammillo-thalamic tracts on the HS and contralateral side were compared between patients and age-matched controls using a two-sided Wilcoxon signed rank tests. Statistical calculations were done using package R, version 3.2.21.

2. Results

2.1. Visual assessment

Hippocampal sclerosis was unequivocally assessed in all 20 patients. Two patients showed mammillary body, and six patients fornix atrophy. Significant anterior temporal lobe gray white matter demarcation loss was not noted.

2.2. Hippocampus volume

Sclerotic hippocampi were significantly smaller compared to the contralateral side (2934 + 436 vs. 4155 + 500 ml) ($p < 0.01$) and to