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Lateralization of temporal lobe epilepsy using a novel uncertainty analysis of MR diffusion in hippocampus, cingulum, and fornix, and hippocampal volume and FLAIR intensity

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Purpose: To analyze the utility of a quantitative uncertainty analysis approach for evaluation and comparison of various MRI findings for the lateralization of epileptogenicity in mesial temporal lobe epilepsy (mTLE), including novel diffusion-based analyses.

Methods: We estimated the hemispheric variation uncertainty (*HVU*) of hippocampal T_1 volumetry and FLAIR (Fluid Attenuated Inversion Recovery) intensity. Using diffusion tensor images of 23 nonepileptic subjects, we estimated the *HVU* levels of mean diffusivity (MD) in the hippocampus, and fractional anisotropy (FA) in the posteroinferior cingulum and crus of fornix. Imaging from a retrospective cohort of 20 TLE patients who had undergone surgical resection with Engel class I outcomes was analyzed to determine whether asymmetry of preoperative volumetrics, FLAIR intensities, and MD values in hippocampi, as well as FA values in posteroinferior cingula and fornix crura correctly predicted laterality of seizure onset. Ten of the cohort had pathologically proven mesial temporal sclerosis (MTS). Seven of these patients had undergone extraoperative electrocorticography (ECoG) for lateralization or to rule out extra-temporal foci.

Results: *HVU* was estimated to be 3.1×10^{-5} for hippocampal MD, 0.027 for FA in posteroinferior cingulum, 0.018 for FA in crus of fornix, 0.069 for hippocampal normalized volume, and 0.099 for hippocampal normalized FLAIR intensity. Using *HVU* analysis, a higher hippocampal MD value, lower FA within the posteroinferior cingulum and crus of fornix, shrinkage in hippocampal volume, and higher hippocampal FLAIR intensity were observed beyond uncertainty on the side ipsilateral to seizure onset for 10, 10, 9, 9, and 10 out of 10 pathology-proven MTS patients, respectively. Considering all 20 TLE patients, these numbers were 18, 15, 14, 13, and 16, respectively. However, consolidating the lateralization results of *HVU* analysis on these quantities by majority voting has detected the epileptogenic side for 19 out of 20 cases with no wrong lateralization.

Conclusion: The presence of MTS in TLE patients is associated with an elevated MD value in the ipsilateral hippocampus and a reduced FA value in the posteroinferior subregion of the ipsilateral cingulum and crus of ipsilateral fornix. When considering all TLE patients, among the mentioned biomarkers the hippocampal MD had the best performance with true detection rate of 90% without any wrong lateralization. The proposed uncertainty based analyses hold promise for improving decision-making for surgical resection.

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1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most frequent type of refractory focal epilepsy. Among TLE structural abnormality syndromes, mesial temporal sclerosis (MTS) is the best predictor of successful surgery for epilepsy [1–4]. Patients with concordant EEG, seizure semiology, neuropsychology and MRI findings, such as atrophy on T1-weighted MR images and hyperintensity on MR Fluid Attenuated Inversion Recovery (FLAIR) of the hippocampus, ipsilateral to the side of seizure onset, do extremely well with resection of the mesial temporal structures [5–11]. However, many of the patients who do not have clear lateralization by preoperative visual inspection subsequently undergo implantation of intracranial electrodes to determine which mesial temporal lobe is epileptogenic [12]. Unfortunately, such implantation carries significant risks of infection, intracranial hemorrhage and elevated intracranial pressure [13]. Prior research has shown that quantitative analysis may identify asymmetry that is not obvious by visual analysis [14]. Therefore, the need for implantation of intracranial electrodes could be obviated by exploiting quantitative lateralization methods. These methods include quantitative MRI analysis, ictal single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetoencephalography (MEG), MR spectroscopy, EEG-functional MRI, and Diffusion tensor imaging (DTI).

DTI has been investigated as a potential imaging modality for the detection of physiological and pathological changes in white and gray matter structures engaged in an epileptic network. Fractional anisotropy (FA) is a measure of fiber and myelin integrity, whereas mean diffusivity (MD) is a measure of bulk mobility of water molecules in tissues [15]. Most previous studies have reported more global bilateral FA and MD abnormalities in cases of unilateral TLE relative to matched regions in nonepileptic subjects [16–27]. Some have reported the ability of DTI to help identify which temporal lobe is epileptogenic by comparing variations between patients with MTS and nonepileptic controls [28–30]. However, this necessitates calibration with nonepileptic controls if a different MRI scanner is used. Prior studies have not compared the differences between homologous regions in each hemisphere in individual subjects, so that each patient can serve as his or her own control. While much previous work has focused on the temporal lobe, there is an opportunity to identify patients with unilateral MTS by examining extratemporal structures. A variety of imaging attributes, applied to both gray and white matter within such a network, have been used to distinguish the network's constituents and extent in one or both cerebral hemispheres [17,19,21,22,24,25].

The cingulum, fornix, and hippocampus are integral components of Papez' circuit. There is evidence that they reflect activity of the mesial temporal structures [17,18,23,24,28,29]. Their bilateral structure, parasagittal location and prominence make them suitable sites for comparative interhemispheric study of the hemispheric variation of diffusion indices. Our first hypothesis is that hemispheric variation of MD within the hippocampus and FA or MD within any of subregions of cingulum and crus of fornix could be used to confirm the laterality of mesial temporal epileptogenicity. The accrual of such quantitative imaging metrics enhances the confidence of clinical decision-making as it regards surgical candidacy and, in particular, the need for extraoperative ECoG.

In the analysis of hemispherical asymmetry of TLE bilateral structures, an interhemispheric variation of an imaging index in an individual patient must be beyond the minimum detectable value — hemispheric variation uncertainty (*HVU*) — to be interpreted as a true — significant variation [31,32]. None of prior studies in the field which reported to observe a unilateral change in the TLE structures determined whether the observed change was beyond the uncertainty. Without such a determination, the trueness of observed changes should be considered with caution. Therefore, *HVU* analysis is of a significant importance especially for DTI measurements with quite large variability in diffusion indices [32]. Our second hypothesis is that a unified uncertainty-based analogy framework would be useful in comparing different TLE lateralization methods and modalities, including our proposed diffusion-based lateralization methods, as well as hippocampal T_1 volumetry and FLAIR intensity analysis [7,9].

2. Material and methods

2.1. Human subjects and image acquisition

The current research study at Henry Ford Health System is federally regulated and approved by the Henry Ford Health System Institutional Review Board (IRB).

Out of 113 patients with TLE who underwent resection of the mesial temporal structures between June 1993 and June 2009, 100 patients achieved Engel class IA. We included only twenty of them (TLE cohort) in the study (10 females with age 41.8 ± 12.6 (mean $\pm$ standard deviation), 10 males with age 42.0 ± 12.5) which had preoperative DTI imaging. Seven of them had undergone extraoperative electrocorticography (ECoG) to determine epileptogenicity (left vs. right and/or temporal vs. extra-temporal). Ten were noted in pathology reports to have MTS (MTS cohort). Table 1 shows the characteristics of the patients.

Preoperative T1-weighted images of TLE patients were acquired on a 1.5 T or a 3.0 T MRI system (Signa, GE, Milwaukee, USA) using spoiled gradient echo protocol (SPGR). T1-weighted imaging parameters were TR/TI/TE = 7.6/1.7/500 ms, flip angle = 20°, voxel size = 0.781 mm × 0.781 mm × 2.0 mm on 1.5 T MRI, and TR/TI/TE = 10.4/4.5/300 ms, flip angle = 15°, voxel size = 0.39 mm × 0.39 mm × 2.00 mm on 3.0 T MRI.

Preoperative FLAIR images of TLE patients along were also acquired with imaging parameters of TR/TI/TE = 10002/2200/119 ms, flip angle = 90°, voxel size = 0.781 mm × 0.781 mm × 3.0 mm on 1.5 T MRI, and TR/TI/TE = 9002/2250/124 ms, flip angle = 90°, voxel size = 0.39 mm × 0.39 mm × 3.00 mm on 3.0 T MRI.

The diffusion weighted images (DWIs) along with a set of b_0 null images (with b-value = 0 s/mm^2) of TLE patients were acquired using echo planar imaging at 25 non-collinear diffusion gradient directions on a 3 T MRI (GE medical system, Milwaukee, USA) with a matrix of 128 × 128, a voxel size of 1.96 × 1.96 × 2.6 mm^3, and a b-value of 1000 s/mm^2. The side of epileptogenicity was blinded during all lateralization processes. MTS was pathologically confirmed as Ammon's horn sclerosis by the pathologists in our institution.

Forty-eight subjects (23 females with age 33.2 ± 9.5, 25 males with age 31.2 ± 6.6) including twenty-five non-epileptic subjects recruited for a sleep research (numbered 1 to 25 in Table 2) and twenty-three healthy volunteers (numbered 25 to 48 in Table 2) were retrospectively included in this study as nonepileptic control subjects. They underwent the same 3.0 T MRI system with the corresponding imaging sequences and imaging parameters. Forty-five subjects had T1-weighted images, twenty-five of which had FLAIR images and the other twenty had DWIs. The rest 3 subjects had only DWIs. Therefore, total of twenty-three subjects had DWIs (Table 2).

2.2. Image preprocessing

In order to perform an stable and smooth segmentation of the cingulum and fornix, the diffusion-weighted images were interpolated to produce a set of homogeneous voxels (1.96 × 1.96 × 1.96 mm^3) which were used to calculate diffusion tensor, FA, MD, and PDD (principal diffusion direction; eigenvector corresponding to the largest eigenvalue of the tensor).

2.3. Segmentation of the cingulum, fornix, and their subregions

Using previously described segmentation and fiber tracking methods [33], the cingulum and its subregions were bilaterally segmented for both datasets. In brief, the cingulum was segmented using an automatic