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Subfield-specific tractography of the hippocampus in epilepsy patients at 7 Tesla

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ABSTRACT

Purpose: MRI-negative epilepsy patients could benefit from advanced imaging techniques such as high-resolution diffusion magnetic resonance imaging (dMRI). Our aim was to perform hippocampal subfield-specific tractography and quantify connectivity of the subfields in MRI-negative patients. Abnormal connectivity of the hippocampal subfields may help inform seizure focus hypothesis and provide information to guide surgical intervention.

Methods: Hippocampal structural imaging and dMRI was acquired in 25 drug resistant MRI-negative patients and 25 healthy volunteers. The hippocampi of each subject was segmented on high-resolution structural images and dMRI-based probabilistic tractography was performed in each subfield. The degrees of connectivity and fiber densities of the hippocampal subfields were quantified and compared between epilepsy patients and healthy volunteers.

Results: We were able to perform subfield-specific hippocampal tractography in each subject that participated in this study. These methods identified some hippocampal subfields that are abnormally connected in MRI-negative patients. In particular patients suspected of left temporal seizure focus exhibited increased connectivity of certain ipsilateral subfields, especially the subiculum, presubiculum, and parasubiculum, and reduced connectivity of some contralateral subfields, such as CA1 and subiculum.

Conclusions: Our data suggest that the hippocampal subfields are connected in distinct ways in different types of epilepsy. These results may provide important information that could help inform seizure focus hypothesis and in the surgical treatment of MRI-negative patients. These observations suggest that high-resolution dMRI-based tractography of the hippocampal subfields can detect subtle abnormalities in otherwise normal-appearing MRI-negative patients.

1. Introduction

Epilepsy is a common neurological disease, affecting roughly 1% of the population. [1] Approximately 30%–35% of all epilepsy patients have drug resistant epilepsy (DRE) and their seizures cannot be controlled with medications [2,3,4,5]. Neurosurgical intervention is a well-established treatment for patients with DRE [6]. Successful resection of a seizure focus depends electrophysiologic and clinical data as well as lesion identification on pre-surgical magnetic resonance imaging (MRI). However, approximately 25% of epilepsy patients remain "MRI-negative", with no identifiable lesion or abnormality on clinical scans at 1.5 or 3 T field strengths [7,3,8,9]. MRI-negative patients are less likely to achieve seizure freedom after surgical intervention than are MRI-positive patients, and generally have worse prognoses [10,11].

Localizing the seizure onset zone in MRI-negative patients is especially difficult, and may require intracranial monitoring using subdural grids or stereoelectroencephalography (SEEG) depth electrodes to provide spatial information about seizure foci and propagation

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pathways [7,12]. Placements of electrodes are determined using non-invasive tools such as MRI, angiography, and scalp EEG [7,12]. Interestingly, MRI-negative epilepsy can be effectively treated with resective surgery or laser ablation if intracranial monitoring successfully localizes the seizure focus [7,12]. The absence of a visible lesion on clinical imaging scans does not necessarily mean the absence of a focal epilepsy network, and further investigation of the epileptic network could improve surgical planning and ultimately outcome for MRI-negative patients.

Since focal epilepsy has received increasing recognition as a network disease, identifying nodes within the network that contribute to seizure activity is an important area of investigation [14,15]. The hippocampus, an archicortical structure in the medial temporal lobe that is composed of cytoarchitecturally distinct subfields, is recognized as a node often involved within epileptic networks. Although small-world network models of epilepsy have demonstrated that individual subfields within the hippocampus participate in seizure activity in different ways [16], the hippocampus has traditionally been treated as a single structure in imaging and clinical settings [16]. The introduction of ultra-high field MRI scanners, coupled with recent software and imaging development has enabled automated segmentation of the hippocampus *in vivo* [17,18,19]. Previous studies employing segmentation have found subfield-specific volumetric differences in epilepsy patients compared with healthy volunteers, suggesting that certain subfields may be more susceptible to changes caused by the disease than others and/or that lesions in certain subfields may contribute differently to the seizure mechanism [18,19]. In addition to gross volumetric analysis, understanding of connectivity patterns of differing hippocampal subfields may reveal important details regarding epileptogenic abnormality of the subfields. However, such an analysis has not been performed to elucidate changes that may exist in epilepsy patients.

Diffusion magnetic resonance imaging (dMRI) is a powerful MRI modality that enables the noninvasive *in vivo* mapping of white matter microstructure [20,21]. Myelination of neuronal axons restricts the direction of diffusion, such that water molecules diffuse along the long axis of the fibers more rapidly than they do on the transverse axes [22]. This so-called anisotropic water movement can be used to model the fiber orientation distribution within the white matter tracts, derive measures of fiber integrity, and quantify connectivity between brain regions [22]. Ultra-high field scanners, such as those operating at 7 T, provide increased signal to noise ratio (SNR), benefitting dMRI resolution [22], and enabling quantification of hippocampal subfield connectivity.

Since the hippocampus is often the target of epilepsy surgery, characterization of hippocampal subfield connectivity may have significant implications for neurosurgical treatment, especially in temporal lobe epilepsy patients. The extent of temporal resection varies between surgeons, and depends upon variable factors including results of scalp EEG, intracranial EEG, and the preoperative amobarbital (Wada) test [2]. While a more extensive temporal resection maximizes the chances of seizure freedom, it also carries the risk of more severe memory and cognitive deficits [2]. Conversely, less aggressive resection reduces the risk of cognitive deficits but also reduces the likelihood of complete seizure freedom.[2] In addition to the procedures listed above, intraoperative electrocorticography (ECoG) is sometimes used to perform a more tailored resection of the hippocampus, however the prognostic value of this method remains controversial [2].

The purpose of this study was to apply 7 T tractography in epilepsy patients in a subfield-specific manner to measure subtle hippocampal connectomic changes that may occur as part of their disease profiles. Although the hippocampus is primarily composed of gray matter it also contains white matter neurocircuitry that project to limbic and cortical regions, and *ex vivo* rodent studies have suggested that different regions of the hippocampus exhibit distinct diffusion profiles [13]. In this study, we investigate hippocampal subfield connectivity related to the suspected seizure foci. Subfield-specific connectivity findings have not yet been reported in epilepsy patients *in vivo*, but may provide insight into the anatomy of the seizure network, as well as provide valuable clinical information that could be used to help guide surgical intervention and predict outcomes. In particular, using markers of connectivity that can be quantified with dMRI may present a novel method of profiling abnormalities within certain hippocampal subregions, and help guide placement sites of both intracranial electrodes and tissue resection in epilepsy patients considered MRI-negative by conventional imaging techniques.

2. Methods

2.1. Participants

Twenty-five focal epilepsy patients [16 females with mean age of 31.2 years, standard deviation (SD) 8.7 years; 9 males, mean 33.9 years, SD 14.4 years] were recruited through their neurologist at the Epilepsy Center at Mount Sinai Medical Center. All patients were MRI-negative, without abnormality on preceding clinical scans (1.5 or 3 T) and were drug resistant. Suspected seizure focus, EEG data, and postsurgical Engel score [23] for patients who have undergone surgery are provided in Table 1. Patients were age- and gender-matched with neurologically and psychiatrically healthy control participants [16 females: mean 31.7 years, SD 8.1 years; 9 males; mean 34.7 years, SD 12.5 years]. All participants provided written informed consent at the beginning of the study.

2.2. Imaging protocol

All participants were scanned under an Institutional Review Board-approved protocol using a 7 T whole body scanner (Magnetom, Siemens Healthcare, Erlangen, Germany). A SC72CD gradient coil was used (G_{max} = 70 m T/m, max slew rate = 200 T/m/s), with a single channel transmit and 32-channel receive head coil (Nova Medical, Wilmington, MA, USA). The MRI scan included a T_1-weighted MP2RAGE sequence: TR = 6000 ms, TE = 3.62 ms, flip angle = 5°, field of view = 240 × 320 mm^2, slices = 240, 0.7 mm^3 isotropic resolution, scan time = 7:26 min. A coronal-oblique T_2-weighted turbo spin echo (T_2TSE) sequence was included: TR = 6900 ms, TE = 69 ms, flip angle = 150°, field of view = 202 × 202 mm^2, in-plane resolution 0.4 × 0.4 mm^2, slice thickness = 2 mm, slices = 40, time = 6:14 min. A high-angular-resolved diffusion-weighted imaging (HARDI) dMRI sequence was also performed with whole-brain coverage: b = 1200s/mm^2, TR = 7200 ms, TE = 67.6 ms, 1.05 mm isotropic resolution, in-plane acceleration R = 3 (GRAPPA), reversed phase encoding in the AP and PA direction for paired acquisition in 68 directions, with a total acquisition time of 20 min.

2.3. Hippocampal subfield segmentation

Automated cortical reconstruction was performed on the T_1-weighted images using the 'recon-all' function in the Freesurfer (http://surfer.nmr.mgh.harvard.edu) image analysis suite version 6.0. After completing the cortical reconstruction, a multispectral segmentation of the hippocampal subfields [17] was performed using both the T_1-weighted and the T_2-weighted images (Fig. 1). The following subfields were segmented: subiculum, presubiculum, parasubiculum; CA1, CA3, CA4; hippocampal tail, hippocampal fissure; molecular layer, granule cell layer of dentate gyrus (GC-ML-DG), fimbria, hippocampal-amygdala transition area (HATA); and the whole hippocampus. Hippocampal subfield volumes were co-registered using nearest neighbor interpolation to dMRI images using Statistical Parametric Mapping 12 (SPM) in MATLAB (r2017a, The MathWorks, Natick, MA). Qualitative manual inspection of the subfield volumes was performed to ensure proper segmentation and co-registration was achieved.