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Temporal lobe epilepsy affects spatial organization of entorhinal cortex connectivity

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ABSTRACT

Evidence for structural connectivity patterns within the medial temporal lobe derives primarily from postmortem histological studies. In humans and nonhuman primates, the parahippocampal gyrus (PHg) is subdivided into parahippocampal (PHc) and perirhinal (PRc) cortices, which receive input from distinct cortical networks. Likewise, their efferent projections to the entorhinal cortex (ERc) are distinct. The PHc projects primarily to the medial ERc (M-ERc). The PRc projects primarily to the lateral portion of the ERc (L-ERc). Both M-ERc and L-ERc, via the perforant pathway, project to the dentate gyrus and hippocampal (HC) subfields. Until recently, these neural circuits could not be visualized in vivo. Diffusion tensor imaging algorithms have been developed to segment gray matter structures based on probabilistic connectivity patterns. However, these algorithms have not yet been applied to investigate connectivity in the temporal lobe or changes in connectivity architecture related to disease processes. In this study, this segmentation procedure was used to classify ERc gray matter based on PRc, ERc, and HC connectivity patterns in 7 patients with temporal lobe epilepsy (TLE) without hippocampal sclerosis (mean age, 14.86 ± 3.34 years) and 7 healthy controls (mean age, 23.86 ± 2.97 years). Within samples paired *t*-tests allowed for comparison of ERc connectivity between epileptogenic and contralateral hemispheres. In healthy controls, there were no significant within-group differences in surface area, volume, or cluster number of ERc connectivity-defined regions (CDR). Likewise, in line with histology results, ERc CDR in the control group were well-organized, uniform, and segregated via PRc/PHc afferent and HC efferent connections. Conversely, in TLE, there were significantly more PRc and HC CDR clusters in the epileptogenic than the contralateral hemisphere. The surface area of the PRc CDR was greater, and that of the HC CDRs was smaller, in the epileptogenic hemisphere as well. Further, there was no clear delineation between M-ERc and L-ERc connectivity with PRc, PHc or HC in TLE. These results suggest a breakdown of the spatial organization of PHg–ERc–HC connectivity in TLE. Whether this breakdown is the cause or result of epileptic activity remains an exciting research question.

1. Introduction

The medial temporal lobe (MTL) is a historically studied region, which mediates numerous clinically significant cognitive functions including episodic memory. Different neuromedical illnesses, such as temporal lobe epilepsy (TLE), can affect the structure and function of the MTL. Therefore, understanding the unique effects of illness on the structure of MTL circuitry can provide insights into both the pathological process of the disease as well as the neuroanatomical basis of the clinical phenomenology of that disease. Relatedly, studying the effect of disease on the functional anatomy of memory circuits can provide additional insight into the mechanisms of MTL function.

Histological studies have illustrated the intra and interhemispheric connections of the medial temporal lobe circuits. The parahippocampal

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gyrus (PHg) can be subdivided along the rostrocaudal axis into the perirhinal cortex (PRc) and, more posteriorly, the parahippocampal cortex (PHc), with the dividing line roughly corresponding to the collateral sulcus [1]. This distinction is based on the existence of relatively distinct regions of input to the PRc/PHc. The PRc receives primary afferent input from the ventral visual stream [2]. In contrast, PHc input includes multimodal association cortices — parietal, supraoccipital, temporal auditory — as well as somesthetic cortex and the dorsal visual stream.

As the PHc and PRc receive separate streams of input, their efferent projections to the entorhinal cortex (ERc) are also distinct [1, 3]. The PHc projects to the medial ERc (M-ERc), which projects to the dentate gyrus and hippocampal fields CA3 and CA1 via the perforant pathway [4]. Conversely, the PRc projects primarily to the lateral portion of the ERc (L-ERc). The L-ERc then sends afferent connections to different targets in the dentate gyrus, CA3, and CA1 [5]. This pattern of connectivity creates two distinct temporal lobe circuits, which may support behaviorally dissociable memory functions.

While postmortem histology studies have demonstrated the elegant complexities of these MTL memory circuits, our ability to visualize these circuits in vivo has been limited by image resolution and data analysis techniques. Structural neuroimaging studies have successfully visualized large MTL white matter tracts and quantified them using diffusion metrics such as mean diffusivity (MD) and fractional anisotropy (FA) [6–12]. Functional neuroimaging studies have successfully delineated similar MTL circuits [13]. However, there has been limited research into structural connectivity patterns within the MTL. A probabilistic tractography method has been used to investigate patterns of connectivity between the thalamic nuclei and cortex [14], the striatal regions and cortex [15], the amygdala nuclei and cortex [16] as well as the amygdala nuclei and subcortical regions [17]. To the best of our knowledge, ours is the first attempt to use probabilistic tractography to visualize connectivity patterns involving the PRc, PHc, ERc, and HC.

Temporal lobe epilepsy (TLE) is an excellent disease model for the study of MTL structure and function. In the last twenty years, quantitative structural magnetic resonance imaging (MRI) research within patient populations with TLE has revealed volumetric reduction in temporal lobe structures including the temporal neocortex [18], the PHg [19], the ERc [20], and the fornix [21]. More recently, diffusion tensor imaging (DTI) studies have demonstrated white matter integrity changes in patients with TLE in white matter extending into the PHg, within the ipsilateral hippocampus [6], fornix [7, 9], and into the inferior temporal gyrus and deep temporal white matter [9].

A promising DTI analytic tool, probabilistic tractography can be used to perform connectivity-based segmentation of gray matter structures [22]. Boundaries of anatomic structures cannot be easily identified in vivo, even with high resolution MRI. Use of differences in connectivity between adjacent and far structures can be used to identify anatomic boundaries in certain structures. Thus, differences in connectivity will allow structural boundaries to be defined, or segmented. This connectivity-based segmentation has not been used to investigate hippocampal or parahippocampal structures. Also absent has been using connectivity-based segmentation to examine the effect of TLE on white matter structures.

2. Methods

This study was approved by the University of Florida Institutional Review Board as well as the North Florida/South Georgia Veterans Administration Hospital Institutional Review Board. All participants or their legal guardians provided written informed consent using forms approved by the University of Florida Institutional Review Board. In accordance with University of Florida Institutional Review Board, seven individuals 10–26 years of age with physician-verified diagnosis of focal onset seizures of temporal lobe origin (TLE) were recruited from the University of Florida Comprehensive Epilepsy Program. Neuroimaging data from a group of seven age-and-gender-matched healthy control individuals were procured from a collaborator's (DBF) study of white matter integrity. All participants were right handed from birth and native English speakers (Table 1). Participants with TLE had a clinical diagnosis of intractable, medically refractory (i.e., drug resistant) unprovoked focal onset epilepsy — affecting the temporal lobe — according to International League Against Epilepsy (ILAE) criteria for epilepsy diagnosis [23]. As part of a presurgical epilepsy evaluation, participants underwent continuous time-locked video-scalp EEG (phase 2) followed at a later date by continuous time-locked subdural temporal and extra-temporal frontal and parietal lobes electrocorticography (phase 2). All participants were candidates for neurosurgical resection; however, none had undergone any neurosurgical intervention at the time of this study. Exclusionary criteria included diagnosis of neurodegenerative disorder, history of concussion, or traumatic brain injury sufficient to warrant medical attention, previous psychiatric hospitalization, history of substance abuse, current psychotropic medication prescription (except anxiolytics and antidepressants), severe, uncorrected hearing or vision impairment, and pregnancy. Additionally, participants with epilepsy were excluded if structural neuroimaging (T1 or T2 data) revealed abnormalities by 3T brain MRI and/or positron emission tomography (PET); MRI was negative for hippocampal sclerosis (HS), dysplasia, malrotation, and focal neoplasia in all participants. Further, two participants had a history of febrile status epilepticus (FSE) and were negative for herpes virus. Both patients underwent acute 3T MRI and follow-up 3T MRI was obtained approximately one year later. Visual interpretation by two neuroradiologists was supplemented by hippocampal volumetrics, analysis of the intrahippocampal distribution of T2 signal, and apparent diffusion coefficients. Hippocampal T2 hyperintensity occurred acutely after FSE in one participant in association with increased volume. The other patient showed a normal MRI acutely. Follow-up MRI obtained on both children was MR-negative.

Table 1
Tractography participant demographics (N = 14).

	TLE (N = 7)		Control (N = 7)	
	Mean	Standard deviation	Mean	Standard deviation
Age[a]	14.8	3.3	23.9	3.0
Sex	5 males	2 females	5 males	2 females
Education[b]	9.1	3.9	11.6	1.3
Age at first seizure[b]	10.0	5.4	–	–
Seizure duration[b]	4.8	3.5	–	–

Note. All participants with TLE were classified by current consensus diagnosis of complex partial temporal lobe epilepsy. N = 14.
[a] Current.
[b] Years.

2.1. Imaging protocol

Participants with TLE in this study underwent an MRI acquisition protocol currently employed in the University of Florida Comprehensive Epilepsy Center. For this protocol, T1-weighted structural data were used for manual segmentation of region of interests (ROIs). T1-weighted, T2-weighted, and Fluid attenuated inversion recovery (FLAIR) data were used to assess hippocampal sclerosis (used for secondary exclusion). The 64-direction high angular direction diffusion imaging (HARDI), as well as 6-direction with three b0 images, was acquired for all participants.

Diffusion-weighted imaging (DWI) and T1-weighted imaging data were collected using a 32-channel head coil on Siemens Magnetom 3T scanner (Siemens Medical Solution, Erlangen, Germany) at the University of Florida Shands Hospital Neuroimaging Center (Gainesville, Florida). Structural Magnetization Prepared Rapid Echo Gradient Image (MP-RAGE) T1-weighted scans were acquired with 120–1.0 mm sagittal slices, Field of View (FOV) = 256 mm (AP) × 192 mm (FH), matrix = 256–192, TR = 450.0 ms, TE = 10.0 ms, Flip Angle = 8, voxel size = 1.0 mm × 0.94 mm × 0.94 mm. Diffusion-weighted images were acquired using a single-shot spin-echo planar imaging (EPI) with 60× 2.0-mm