Functional Asymmetry of Hippocampal Subfields in Tempoal Lobe Epilepsy: An Application of Postmortem Atlas

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Introduction

Functional lateralization of cognitive function is an important step in the presurgical evaluation of patients with refractory unilateral temporal lobe epilepsy (TLE). BOLD fMRI has been advanced as a possible non-invasive alternative to the invasive IAT (Intracarotid Amobarbital Test) based language lateralization [1], but its usefulness has been limited for memory lateralization [2]. Asymmetry indices based on ROI (region of interest) based activation differences have been proposed using the whole hippocampus as well as larger temporal lobe ROIs [3]. However, TLE, like many other diseases affecting the hippocampus, presents with differential involvement of hippocampal subfields. Thus, asymmetry indices based on hippocampal subfields may be more powerful for memory lateralization than those using larger, inhomogeneous ROIs. *Here we present, for the first time, an analysis of activation asymmetry in TLE patients across different hippocampal subfields.*

Methods

Eighteen subjects with TLE were imaged in a 3 Tesla Siemens Trio scanner using an eight-channel head coil and body coil transmitter. T1-weighted structural MRI scans were obtained using the MP-RAGE sequence with the following parameters: TR=1620 ms, TE=3.87 ms, TI=950 ms, flip angle=15^0, and voxel size=0.9375x0.9375x1 mm. BOLD fMRI images were obtained using a gradient echoplanar (EPI) sequence with TR=3000 ms, TE=30 ms, and 3-mm isotropic voxels during a blocked design experiment consisting of a memory encoding task (see details in [4]).

The EPI data were motion corrected, aligned to the structural image, and a general linear model was used to generate activation maps using Statistical Parametric Mapping (SPM5) software [5]. The contrast images were sampled within 6 different hippocampal subfield labels (Head, CA1, CA2, CA3, Dentate Gyrus (DG), Tail). The subfields were labeled in the anatomical image by using shape-based normalization of the subject's whole hippocampus to a postmortem hippocampus atlas [6] containing subfield labels. Task contrast was integrated over each subfield and pairwise t-tests were conducted between activations in the epileptogenic (ipsilateral to seizure focus) side and the non-epileptogenic (contralateral to seizure focus) side within different subfields, yielding measurements of subfield-level activation asymmetry.

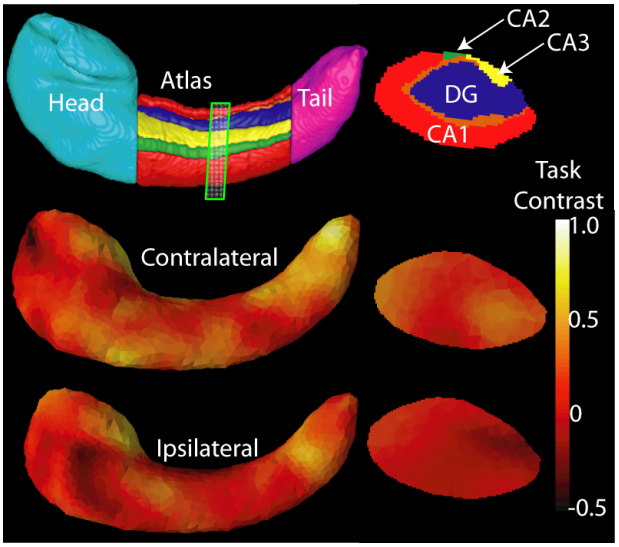

Figure 1: Postmortem atlas labels (top) and mean task contrast map within the hippocampi of TLE patients ipsilateral and contralateral to seizure focus, projected onto the atlas space. Green plane shows the location of transverse cuts shown on the right.

Subfield	Mean Contrast (Contralateral)	Mean Contrast (Ipsilateral)	p-value (Contralateral> Ipsilateral)
CA1	11491	6916	0.003
CA2	274	265	0.13
CA3	771	407	0.02
DG	8369	3814	0.0008
Head	42429	20864	0.0002
Tail	12560	6793	0.003

Table 1: Average integrated task contrast across hippocampal subfields in the contralateral and ipsilateral sides. Units are arbitrary. Numbers can be compared between the two sides.

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Results

Mean local activation within the contralateral hippocampi is generally greater than that in the ipsilateral hippocampi as expected (Figure 1). Activation within each hippocampal subfield except CA2 is significantly greater on average in the contralateral side. The strongest effects are seen in the hippocampus head and in the dentate gyrus. Figure 2 shows paired plots of activation in contralateral vs. ipsilateral side for these two subfield labels. Table 1 lists the mean integrated task contrast values within each subfield and the corresponding t-statistics from paired t-tests signifying greater activation in the contralateral side than the ipsilateral side.

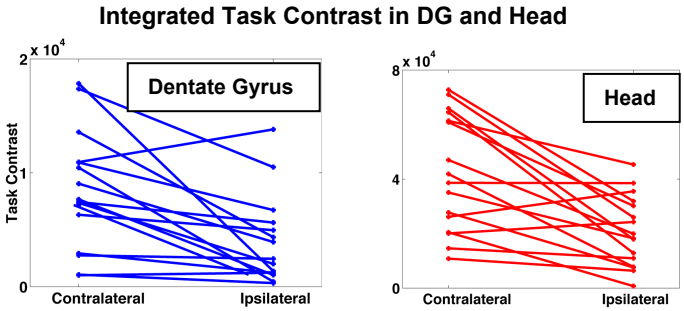

Figure 2: Pairwise task contrast values integrated over DG (blue) and head (red) subfields. Each line represents data from one subject. Most of the lines slope downwards form left to right, indicating lower subfield activation in the subjects' epileptogenic side.

Discussion

To our knowledge, this is the first clinical study of TLE to examine hippocampal activation at a subfield level. Several studies of hippocampal atrophy in TLE have found greater disease effects in dentate gyrus [7] and the anterior hippocampus region, which is subsumed in the head label. Note that our subfield labels are derived with only a shape-based normalization without using any intensity information from the anatomical scan, as the subfields are not distinguishable in standard T1-weighted clinical MRI. Yet, we do find strong activation asymmetry effects in DG and head, consistent with imaging as well as histological findings. Using subfield level measurements may provide better localization and lateralization of memory function in TLE. Future work will further investigate their utility in presurgical planning as well as predicting postoperative cognitive outcome.

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