# Functional Activation Within Hippocampal Subfields During Scene Memory Encoding In Temporal Lobe Epilepsy

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## Introduction

*We present, for the first time, functional activation patterns within hippocampal subfields in temporal lobe epilepsy (TLE) patients.* The hippocampus is a complex structure consisting of subregions that express varied cell types, and are differentially affected by neurological disorders, including TLE. For example, dentate gyrus (DG) is one subfield that has been implicated in both histological [1], and more recently, in structural imaging studies [2] as an epileptogenic site. While functional activation as well as inter-hemispheric functional asymmetry within the larger whole hippocampal region of interest (ROI) has been shown to have predictive value for cognitive outcome following epilepsy surgery, as well as in pre-surgical lateralization of function, more focal functional measurements within subfield ROIs haven't yet been studied. We use an atlas-based method to label subfields in structural MRI and report functional activation within these ROIs. We detect group differences in subfield activation between controls and patients and between patients' epileptogenic and non-epileptogenic sides, as well as differential activation of DG and CA1 in controls, but not in patients.

## Methods

Eighteen subjects with refractory TLE and 19 healthy controls 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=0.94x0.94x1 $mm^3$. 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 complex scene memory encoding task (see details in [3]).

A binary segmentation of the whole hippocampus is obtained from the subject's anatomical MRI using the method described in [4]. Six hippocampal subfield ROIs (Head, CA1, CA2, CA3, DG, Tail) were then labeled using shape-based normalization of this whole hippocampus mask to a postmortem hippocampus atlas [5] containing subfield labels. This mapping preserves the relative depth of structures in the subject space. Head and Tail were given separate labels as it's harder to distinguish individual subfields in these regions. The EPI data were motion corrected, and then aligned to and resampled in the high-resolution space of the structural MRI, which helps increase the effective resolution of measured activation [6]. We do not perform any spatial smoothing, which helps preserve spatial specificity. A general linear model was used to generate task activation maps using Statistical Parametric Mapping (SPM5) software [7]. The contrast images (Fig. 1) were sampled within the subfield ROIs. Task contrast was integrated over each subfield to generate ROI-based activation measurements.

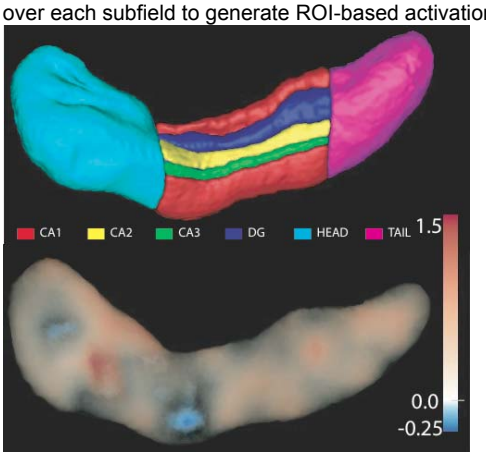


**Figure 1:** Example of subfield labels in a 3D rendering of the hippocampus (top) and task activation map (bottom). Hotter color indicates greater task-related activation.

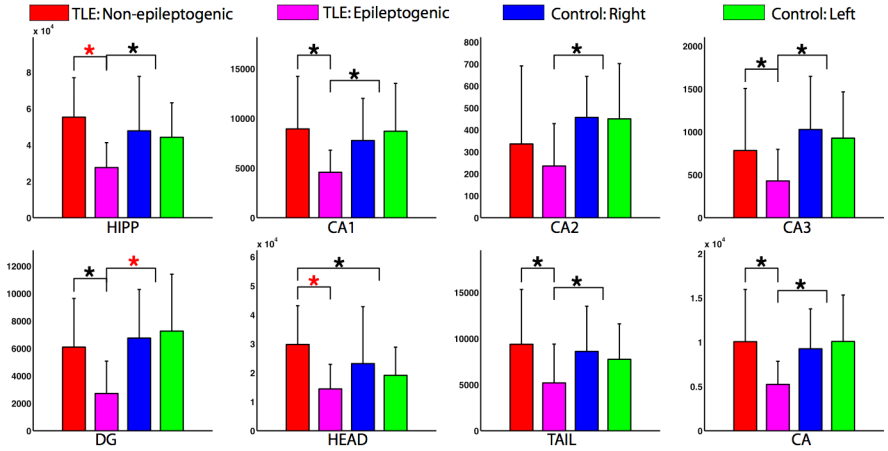


**Figure 2**: Functional activation within subfields in patients' non-epileptogenic (red) and epileptogenic (magenta) sides, and in controls' right (blue) and left (green) sides. Stars indicate significant group differences in activation ($p<0.05$). Red stars denote the most significant effects ($p<0.0001$). Group comparison between either side in patients and controls used activation averaged over left and right side for the control group.

## Results

Figure 2 plots group-wise functional activation in subfields as well in whole hippocampus. No subfields showed significant activation differences between left and right sides in controls. However, most subfields showed greater activation in controls (averaged over left and right) as well as in the non-epileptogenic side in patients than in the epileptogenic side in patients. The biggest effects were found in DG, Head and whole hippocampus (HIPP). Patients' non-epileptogenic side had greater activation than controls in the Head region. We also compared activation between DG and CA1, as DG has been shown to be selectively active during encoding [8]. Controls had significantly greater activation in DG in both hemispheres ($p<0.001$ on both sides, paired t-test), an effect that was not present in either hemisphere in patients.

## Discussion

This study demonstrates that subfield-specific group differences in functional activation during an episodic memory task between controls and TLE patients and between hemispheres in patients can be detected. Largest effects in DG and Head are consistent with recent structural morphometry literature [2]. Effects in Head may be partly attributable to the inclusion of some portion of DG in the Head label. Interestingly, we found greater activation in Head in patients' non-epileptogenic side than controls, which may indicate compensatory mechanisms in the healthy side. We also found DG to be more active during scene encoding than CA1 in controls, similar to effects reported in [8]. However, patients do not show this effect, possibly due to activation in DG being affected by pathology. Recall that DG also showed the greatest group effects in activation. Abnormal sprouting of mossy fibers, which connect DG and CA3, has been reported in histological studies [1]. These are preliminary results, and will need be validated in a larger dataset, particularly for exploring the predictive value of subfield-specific measurements by correlating with cognitive outcome variables in surgical patients. Also, because of the presence of sclerosis in some patients, some of the functional effects may reflect underlying structural atrophy. Future work will also include improvements in spatial resolution of both structural and functional MRI to better localize activation within small subfield ROIs.

**References**:
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