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The gamma band effect for episodic memory encoding is absent in epileptogenic hippocampi

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HIGHLIGHTS

- Oscillatory patterns during episodic memory encoding in the human hippocampus are altered in epileptogenic hippocampi.
- The gamma band effect, a robust pattern observed in non-epileptogenic hippocampi, is reversed in epileptogenic hippocampi.
- This pattern in epileptogenic hippocampi may reflect active suppression during episodic item encoding.

ABSTRACT

Objective: The analysis of hippocampal local field potentials in humans during the encoding of episodic memories has revealed that a robust increase in gamma band oscillatory power predicts successful item encoding, termed the gamma band subsequent memory effect (SME). No previous investigation has looked for differences in this pattern between epileptogenic and non-epileptogenic sources; we sought to examine the gamma band effect in seizure patients to address this question.
Methods: We recorded hippocampal activity in nine patients who underwent stereoelectroencephalography for seizure localization and also performed the Free Recall task, a standard test of episodic memory. We compared gamma band oscillatory activity between 15 electrodes localized to epileptogenic hippocampi and 24 electrodes in non-epileptogenic hippocampi.
Results: The epileptogenic hippocampi exhibited a significant decrease in gamma band power during successful item encoding, whereas the non-epileptogenic group exhibited the expected positive gamma band effect ($t(37) = 4.69$, $p < 0.0001$).
Conclusions: The typical gamma band effect is reversed for epileptogenic hippocampi.
Significance: This is the first study to demonstrate a difference for epileptogenic hippocampi for an important oscillatory pattern that normally predicts successful item encoding. Patients with epilepsy suffer selective impairment of episodic memory ability, so our findings are especially relevant for clinicians and memory researchers alike.

1. Introduction

Episodic memory, in which specific memory items are placed within temporal context during encoding and retrieval, strongly depends on the contribution of the hippocampus (Burgess et al., 2002; Tulving, 2002). Correspondingly, episodic memory shows selective and marked degradation in patients with temporal lobe epilepsy (Dupont et al., 2000). The implantation of electrodes in

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human patients to localize seizures has provided memory researchers with the opportunity to explore patterns of brain activity that occur during episodic memory encoding with high spatial and temporal resolution (Jacobs and Kahana, 2010). By comparing features of brain activity during successful versus unsuccessful item encoding, researchers can identify oscillatory patterns that uniquely predict memory formation (Sederberg et al., 2003; Sederberg et al., 2007). These patterns are termed subsequent memory effects (SME).

In the human hippocampus, the most robust and consistent SME is an increase in gamma band (40–200 Hz) oscillatory power during successful item encoding (Sederberg et al., 2007). This gamma band effect is considered a *positive* SME because power is relatively higher when memories are formed versus when they are not. At other frequency bands by contrast, changes in power often show the opposite pattern, with decreased power during successful encoding (a *negative* SME). Using invasive recordings, a hippocampal gamma band effect has also been observed during working memory tasks, spatial navigation, and autobiographical memory in human participants (Ekstrom et al., 2005; Fell et al., 2001; van Vugt et al., 2010; Axmacher et al., 2007). These studies have generally excluded abnormal hippocampi, especially epileptogenic hippocampi, because these investigations typically seek to establish generalizable human patterns analogous to animal data. There is evidence of diminished BOLD responsiveness in abnormal hippocampi in epilepsy patients during episodic memory; this effect may predict memory decline after surgery (Jokeit et al., 2001). An analysis of recognition memory in epilepsy patients identified differences in interictal spiking throughout the brain for recognized memory items, suggesting that memory processes interact with epileptic networks at the neurophysiological level (Matsumoto et al., 2013). However, no direct comparison of the gamma band SME between epileptogenic and non-epileptogenic hippocampi has been undertaken.

To examine the gamma band SME in epilepsy, we analyzed a set of nine patients (ten hippocampal implantations, age 18–62, seven female) who underwent stereoelectroencephalography (sEEG) for seizure localization and then performed an episodic memory task. We compared activity during the encoding of episodic memories between epileptogenic and non-epileptogenic hippocampi, hypothesizing that the gamma band SME would be absent or diminished in the epileptogenic hippocampi. We demonstrate that gamma band activity is significantly different between the two groups: in epileptogenic hippocampi gamma power *decreases* during successful item encoding, while non-epileptogenic hippocampi exhibit the expected + SME. We discuss some theoretical underpinnings and implications for this finding.

2. Methods

Electrode implantation was performed using the ROSA stereotactic robot after a double-contrast high resolution volume acquisition MRI (Gonzalez-Martinez et al., 2013). Patients were tested from 48 h after implantation when clinical obligations permitted and when they had not suffered seizure activity for at least four hours while awake and fully able to participate. Sessions were not initiated if patients were drowsy or otherwise unwilling to engage in the task. Sessions in which a patient suffered a seizure during testing were not included (one session across all participants). In general, sessions occurred at the beginning or end of an implantation period, when patients were on medication and interictal activity was subdued. Informed consent governed by the principles of the Declaration of Helsinki with a protocol approved by the Cleveland Clinic IRB was obtained. Participants performed the Free Recall task, described in Fig. 1A with a subsequent memory paradigm (Paller and Wagner, 2002). Electrode locations were confirmed by co-registration of postoperative CT with MRI scans using Freesurfer software with personal review by the senior neurologist author (IN) with neuroradiology confirmation (Fischl, 2012). Electrode locations were confirmed via direct cortical stimulation when possible (e.g. when in primary sensory cortex). Data were sampled at 1000 Hz. A local average re-reference that excluded electrodes exhibiting interictal or ictal activity was used. An additional analysis using a bipolar reference paradigm is included in the Supplementary Material. Initially, power was extracted for each frequency in the spectrum using Morlet wavelets (log spaced from 2 to 200 Hz) and plotted for recalled and non-recalled events separately. For statistical comparison, power in the 40–70 Hz low gamma and 70–200 Hz high gamma band were extracted separately using the Hilbert transform for the 1800 ms interval following item presentation (250 ms buffer, notch filtered at 60 Hz). Gamma power was normalized and then averaged across the time series (van Vugt et al., 2007). A normalization period in which participants looked at a fixation cross immediately prior to the beginning of each list was used. A kurtosis methods was used to reject artifacts, including interictal spiking activity (threshold of 5). A more detailed discussion of the kurtosis methods and the impact of its implementation on our data is available in the Supplementary Material. The rank sum test was used to derive a W statistic that was compared to a distribution of 1000 W statistics generated by randomly shuffling recalled and non-recalled power values. A z statistic was extracted for each electrode by transforming the p value generated by determining the position of the true W statistic among the 1000 W statistics from the dummy distributions (Sederberg et al., 2003). This resulted in a distribution of z values for epileptic and non-epileptic hippocampi (one for each electrode), to which we applied a two-group t-test. Final p values from this test were then Bonferroni corrected for the two frequency bands tested.

Seizure onset locations were determined by re-review of sEEG recordings in Nihon-Kohden software prior to data analysis. In all cases, the timing (or absence of) hippocampal involvement could be accurately characterized. Side of hemispheric dominance was gleaned from clinical records (i.e. Wada, fMRI, handedness) included in standard pre-implantation evaluation and checked via consensus of the participating epileptologist and operating surgeon. The presence and nature of interictal activity was assessed. An example seizure for a patient with hippocampal onset is included in Fig. 2.

3. Results

To directly compare the gamma band subsequent memory effect between epileptogenic and non-epileptogenic hippocampi, we recorded hippocampal activity from nine patients undergoing pre-operative sEEG for seizure localization (eight unilateral, one bilateral implantation). The patients received an average of 10.6 implanted arrays, all inserted with millimeter accuracy using the ROSA stereotactic robot (Gonzalez-Martinez et al., 2013). The ictal onset location and pattern of spread were determined via standard extraoperative seizure monitoring. Three patients (15 electrodes) exhibited hippocampal onset, while in the remaining six patients ictal onset was outside the hippocampus (24 electrodes). Table 1 describes participant characteristics, seizure onset, timing of hippocampal spread, and interictal spike frequency.

During the extraoperative recording period, the patients performed the Free Recall task (Fig. 1A), a standard test of episodic memory. Participants performed an average of 2.1 sessions of Free Recall during the testing period. Serial position curves (Laming,