

# Declarative memory formation in hippocampal sclerosis: an intracranial event-related potentials study

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The functional deficits associated with hippocampal sclerosis during declarative memory formation are largely unknown. In this study, we analyzed intracranial event-related potentials recorded from the medial temporal lobes of nine epilepsy patients performing a word memorization task. We used frequency-specific wavelet analysis to assess stimulus-related changes in power and intertrial phase coherence. Statistical analysis revealed a significant decrease of stimulus-induced power in the  $\delta$  and  $\theta$  range on the side of

pathology. No significant differences in phase locking were observed. Findings indicate a reduced availability of recruitable neural assemblies not only in the hippocampus but also in the rhinal cortex during memory formation. Network functions related to the timing of neural responses to the stimulus appear to be preserved. *NeuroReport* 18:317–321 © 2007 Lippincott Williams & Wilkins.

**Keywords:** declarative memory, epilepsy, event-related potentials, hippocampal sclerosis, intracranial electroencephalogram

## Introduction

Hippocampal sclerosis is the most frequent pathological finding associated with temporal lobe epilepsy. Histopathologically, hippocampal sclerosis is characterized by gliosis and severe neuronal degeneration, particularly in the CA1 and CA3 region and the hippocampal hilus [1]. Apart from the clinical manifestation of seizures, the main neuropsychological correlate of hippocampal sclerosis is an impairment of long-term memory functions [2]. To date, there is no study directly investigating the influence of hippocampal sclerosis on memory formation by means of intracranial event-related potentials (ERPs).

The waveforms observed in ERPs, such as the N400 of the anterior medial temporal lobe (AMTL-N400) or the hippocampal P300, can be caused either by stimulus-evoked increase in electroencephalogram (EEG) power or by increased intertrial coherence (phase clustering) of the ongoing EEG activity [3–7]. Stimulus-evoked power changes are thought to correspond to the event-related activation of neural assemblies distinct from ongoing background dynamics. On the other hand, stimulus-related phase entrainment of ongoing oscillatory activity can produce an ERP component without additional recruitment of activated neurons.

In this study, we therefore apply wavelet-based time-frequency analysis and circular phase statistics to event-related EEG signals recorded intracranially from the medial

temporal lobes of epilepsy patients to resective surgery performing a long-term memorization task. By separating effects of power (amplitude) and coherence (phase), we aim to shed light on the mechanisms involved in the functional deficits of the structures involved in the epileptic process.

## Methods

### Subjects

Nine patients (six women; mean age  $34.1 \pm 8.3$  years) with pharmacoresistant unilateral temporal lobe epilepsy participated in the experiment. In six patients, seizures originated exclusively from the right medial temporal lobe; in three patients, exclusively from the left medial temporal lobe. After resection of the epileptic medial temporal lobe, all patients remained seizure-free (follow-up, 6–15 months). In all patients, histopathological examination of resected tissue revealed hippocampal sclerosis. The EEG study was approved by the local medical ethics committee. Each patient gave written informed consent.

### Experimental paradigm

Patients performed a word list memorization paradigm with a free recall test during EEG recording [8]. Each patient participated in 20 blocks, consisting each of a study, a distraction, and a test phase. During each study phase, 12 words were sequentially presented in uppercase letters on a

computer screen for a duration of 400 ms. Interstimulus intervals were randomized and ranged from 2.3 to 2.7 s (mean 2.5 s). To prevent ongoing rehearsal, a distraction task (counting backwards by threes) was conducted after each study phase (duration 30 s). Immediately after this distraction task, patients were asked to recall freely and in any order the 12 words previously displayed. Stimuli consisted of 240 semantically unrelated nouns with a mean length of six letters (range: 4–11) and a mean word frequency of 75 per million (range: 15–175 per million).

#### Intracranial electroencephalogram recording

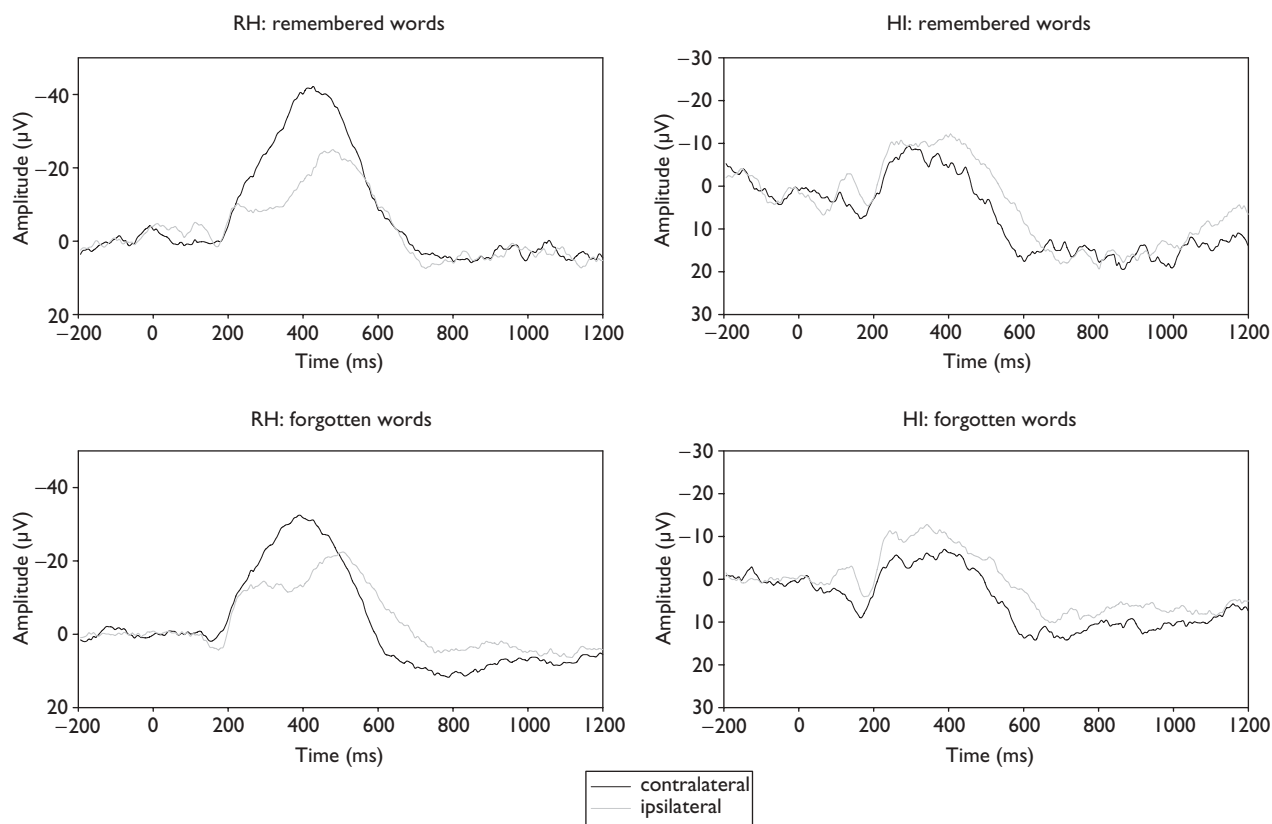
Bilateral depth electrodes, each equipped with 10 contacts, were inserted along the longitudinal axis of the hippocampal formation using a computed tomography-based stereotactic insertion technique [9], with the anterior contacts located in the anterior parahippocampal gyrus, which is covered by rhinal cortex, and the posterior contacts located within the hippocampus (cf. [8]). Depth electrode recordings were necessary before resective surgery because the seizure onset zone could not be determined unequivocally from surface recordings. The location of electrode contacts was ascertained by MRI in each patient. MRI scans were acquired in sagittal and adjusted coronal (perpendicular to the longitudinal axis of the hippocampus) and axial (parallel to this axis) planes, and anatomical boundaries were ascertained according to Insausti *et al.* [10].

Depth electroencephalograms were referenced to linked mastoids, band-pass filtered (0.03–85 Hz, 6 dB/octave), and

recorded at a sampling rate of 173 Hz (12-bit analog–digital conversion). EEG data for the 240 trials were scanned for artifacts in each patient; 14.4% of trials (range: 1.3–46.7%) were discarded for the focal side (the side containing the seizure-generating focus) and 5.3% (range: 1.7–10.0%) for the nonfocal side. In each hemisphere, one rhinal and one hippocampal electrode contact were selected for further analysis. Selection criterion was highest amplitude of the rhinal AMTL-N400 and the hippocampal late positive component (LPC), respectively [11].

#### Analysis of power changes and phase clustering

EEG trials were filtered in the frequency range from 0.5 to 30 Hz (0.5 Hz steps) by continuous Morlet wavelet transforms [12–14]. The number of cycles of the Morlet wavelet governs the bandwidth of the wavelet filter around a given center frequency and was adapted to yield a constant bandwidth of 1 Hz at full-width at half-maximum for each of the 30 bands, so frequency bands overlapped by 50%. From the wavelet-transformed signals, the phases and power values were extracted for each time point of each trial and were subsequently used to calculate intertrial phase clustering (phase locking) and power changes as described in [7]. Power and phase locking values were normalized with respect to a prestimulus time window of 200 ms separately for each participant and each filter frequency. For the graphical depiction, normalized power and phase-locking values were averaged over patients and then transformed into decibel scale.



**Fig. 1** Medial temporal lobe depth recordings in a memorization paradigm for the focal (grey) and nonfocal (black) side. Left: grand average of event-related potentials (ERPs) from within the rhinal cortex (with the AMTL-N400 as most prominent component) for remembered and forgotten words, respectively. Right: grand average of ERPs from within the hippocampus (with the late positive component as most prominent component).

**Statistical analysis**

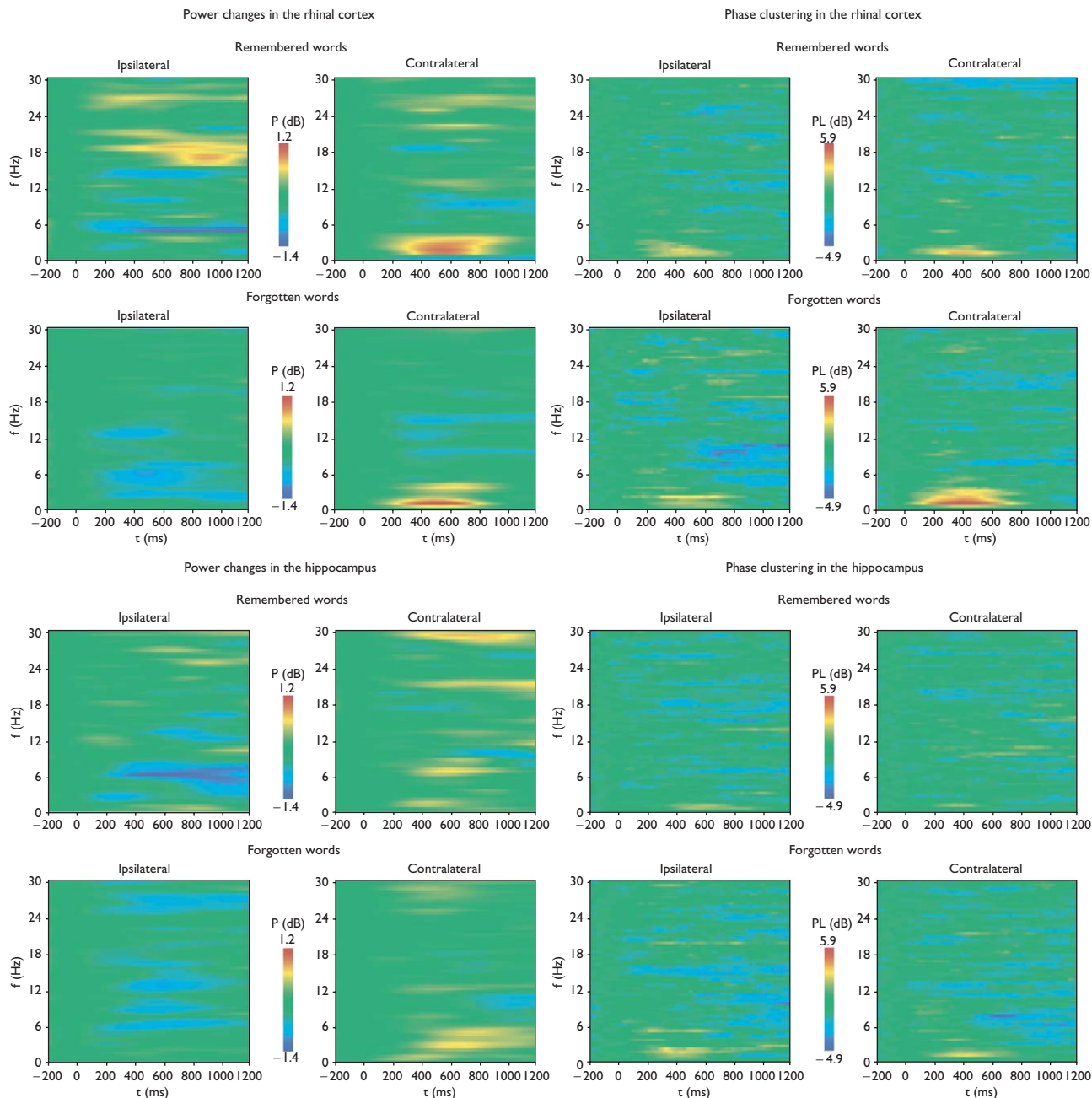
We extracted the peak amplitudes of the ERPs for the rhinal AMTL-N400 (time range: 200–600 ms) and for the hippocampal LPC (500–1200 ms). We averaged the normalized power and phase-clustering values for each patient over the same time range and a frequency range from 1 to 7 Hz. We then conducted a three-way analysis of variance with locus (rhinal vs. hippocampal), memory (subsequently remembered vs. forgotten words), and pathology (focal vs.

nonfocal) as repeated measures. Dependent variables were power, phase clustering, and absolute values of ERP peak amplitudes, respectively.

**Results**

**Performance**

Mean recall rate of the previously displayed words was 29.7%. Individual recall rates ranged between 20.0 and 54.6%.



**Fig. 2** Grand average of power changes (left panel) and changes in phase clustering (right panel) in the rhinal cortex (upper part) and hippocampus (lower part) for subsequently remembered (rows 1 and 3) and forgotten words (rows 2 and 4) for event-related potentials recorded from the ipsilateral (focal, columns 1 and 3) and contralateral (nonfocal, columns 2 and 4) temporal lobes. The plots show color-coded power values and phase-locking values, which have been normalized with respect to a prestimulus baseline of 200 ms and transformed into decibel scale ( $10 \cdot \log_{10}$ ). The different frequencies (0.5–30 Hz) are represented on the ordinate, whereas time relative to the onset of stimulus presentation is depicted on the abscissa.

### Average event-related potential waveforms

We observed a decrease in ERP amplitudes on the pathological vs. the contralateral side for AMTL-N400 and to a lesser extent for the hippocampal LPC (Fig. 1). Statistical analysis revealed a main effect for memory [ $P < 0.012$ ;  $F(1, 8) = 10.22$ ] with increased amplitudes for subsequently remembered vs. forgotten words and a statistical trend for pathology [ $P = 0.057$ ;  $F(1, 8) = 4.93$ ]. No significant interactions were observed.

### Power changes

Figure 2 (left panel) depicts the grand average of power changes [remembered vs. forgotten words, ipsilateral (focal) vs. contralateral (nonfocal) side, rhinal cortex vs. hippocampus]. Note an increase in power in the  $\delta/\theta$  band (1–7 Hz) on the nonfocal side during memory formation, which appears more pronounced in the rhinal cortex than in the hippocampus. In contrast, averaged  $\delta/\theta$  power dropped below the prestimulus baseline on the focal side, although this effect was not statistically significant. Statistical evaluation yielded a significant effect only for pathology [ $P < 0.01$ ;  $F(1, 8) = 11.25$ ], whereas no significant effects were found for memory and locus. In particular, there was no significant interaction of locus\*pathology [ $P > 0.225$ ;  $F(1, 8) = 1.73$ ], which confirms that a significant decrease in power was observed both in the hippocampus and the rhinal cortex.

### Phase clustering

Figure 2 (right panel) depicts the phase clustering averaged over patients. Note the increase in phase clustering in the  $\delta/\theta$  range, which is more pronounced in the rhinal cortex than in the hippocampus. Statistical evaluation yielded a main effect for locus [ $P < 0.003$ ;  $F(1, 8) = 18.05$ ]. No significant effects were found for memory and pathology, and no significant interactions were observed.

### Discussion

In this study, we analyzed power/phase effects in rhinal and hippocampal ERPs recorded from the epileptic and contralateral medial temporal lobe in epilepsy patients with unilateral hippocampal sclerosis during declarative long-term memory formation. Although in healthy humans with typical language dominance declarative memory is considered to be a predominant function of the left hippocampus, this assumption is not valid for patients with left hippocampal sclerosis, who exhibit an increased incidence of atypical language lateralization [15]. We therefore did not distinguish between right- and left-hemispheric pathology in this study. Successful memory formation is accompanied by a significant increase in the rhinal AMTL-N400 and the hippocampal LPC [11]. Interestingly, this effect is not accompanied by a significant increase in either power or phase clustering, suggesting that a combination of phase clustering and power changes produces the amplitude effect observed in the average ERP.

As the main finding we observed a statistical trend for decreased ERP amplitudes on the focal side in comparison with the nonfocal side, which is reminiscent of findings reported using other cognitive paradigms [16–18]. Phase/power analysis revealed that this reduction of amplitudes in the pathological temporal lobe is caused by a significant

decrease in  $\delta/\theta$  power. After stimulus presentation, the power on the pathological side even tends to drop below the prestimulus baseline.

This decrease in power probably reflects a lower number of neural assemblies that are being recruited into the memorization task. The most likely reason for this is a decreased availability of neural assemblies owing to the neuronal degeneration associated with hippocampal sclerosis [1]. Interestingly, this effect is not restricted to the hippocampus, but is equally present in the rhinal cortex. The latter finding is in disagreement with a recent neuropathological examination of entorhinal cortical tissue that did not confirm a stereotypical neuronal loss pattern in patients with hippocampal sclerosis [19]. Our findings thus indicate that although principal neurons may still be present in the rhinal cortex, they may not necessarily be available any more for memory processing or may require reciprocal hippocampal interaction for this process.

The missing influence of the side of pathology on the phase clustering, on the other hand, indicates that the network functions of the remaining neuronal assemblies are not impaired and that the timing of their stimulus-related recruitment remains rather accurate. As hippocampal phase locking is considered to depend on external input from the rhinal cortex [20], this finding suggests that the rhinal cortex continues to project onto the sclerotic hippocampus [21].

### Conclusion

Power/phase analysis of intracranial ERPs in hippocampal sclerosis indicates a reduced availability of recruitable neural assemblies not only in the hippocampus, but also in the rhinal cortex during declarative memory formation. Network functions related to the timing of neural responses to the stimulus appear to be preserved.

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