Brief Communications

# Medial Temporal Theta/Alpha Power Enhancement Precedes Successful Memory Encoding: Evidence Based on Intracranial EEG

**Juergen Fell,[1] Eva Ludowig,[1,3] Bernhard P. Staresina,[1,4] Tobias Wagner,[1] Thorsten Kranz,[1] Christian E. Elger,[1,2] and Nikolai Axmacher[1]**

[1]Department of Epileptology, University of Bonn, D-53105 Bonn, Germany, [2]Life and Brain Center of Academic Research, University of Bonn, 53127 Bonn, Germany, [3]Department of Psychology, University of Düsseldorf, 40225 Düsseldorf, Germany, and [4]Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, CB2 7EF Cambridge, United Kingdom

**Not only poststimulus, but also prestimulus neural activity has been shown to be predictive for later successful memory encoding. However, it is still not clear which medial temporal lobe processes precede effective memory formation. Here, our aim was to investigate whether such prestimulus markers for successful memory encoding can be specified based on intracranial recordings directly from the hippocampus and rhinal cortex. For this purpose, we analyzed subsequent memory effects during a continuous word recognition paradigm in 31 presurgical epilepsy patients. We found that rhinal and hippocampal theta and successive alpha power enhancement before word presentation predicted successful memory encoding. Previous studies suggest that stimulus-triggered hippocampal theta activity is particularly related to memory retrieval and activation of a mnemonic context, whereas the alpha rhythm reflects inhibitory top-down control of task processing and executive functioning. In line with these suggestions, we propose that the observed medial temporal theta and alpha power increases before stimulus presentation reflect activation of contextual information and inhibitory top-down control processes preparing for stimulus-triggered memory processing.**

## Introduction

It is well established that the medial temporal lobe (MTL) and, in particular, the hippocampus play a crucial role for declarative long-term memory (Eichenbaum, 2000; Squire et al., 2004). Accordingly, studies using various complementary neuroimaging techniques have revealed evidence for differential activations following subsequently remembered versus forgotten items (for review, see Wagner et al., 1999; Otten and Rugg, 2002; Axmacher et al., 2006; Eichenbaum et al., 2007). In addition to poststimulus effects, it has recently been demonstrated that neural prestimulus activity can also be predictive of successful memory formation. Using functional magnetic resonance imaging, Park and Rugg (2010) found increased hippocampal and parahippocampal activations associated with successful word encoding within the cue-item interval. Similar hippocampal prestimulus effects were described for the learning of reward-predicting images (Adcock et al., 2006) and for the memorization of aversive pictures (Mackiewicz et al., 2006). In two EEG studies, Otten et al. (2006, 2010) demonstrated that a frontal negative modulation occurring up to 1 s before cued words predicts later recollection.

Recently, medial temporal theta (4–8 Hz) activity shortly before word presentation (starting −200 ms) has been shown to precede successful encoding as inferred from source-reconstructed magnetoencephalography (MEG) recordings (Guderian et al., 2009). Theta oscillations represent a putative basis for hippocampus-dependent memory processing (Kahana et al., 2001; Buzsáki, 2005), and stimulus-triggered theta activity seems to be particularly related to memory retrieval (Klimesch et al., 2001; Guderian and Düzel, 2005; Osipova et al., 2006). Therefore, Guderian et al. (2009) interpreted the prestimulus enhancement of theta-band activity associated with successful encoding as indicating the activation of a mnemonic context, in which the subsequently presented item can be embedded. However, MEG-based localization of activity from deep brain structures is prone to considerably higher uncertainty compared with neocortical sources (Tarkiainen et al., 2003; Santiuste et al., 2008).

Therefore, our aim was to investigate whether such prestimulus markers for successful memory encoding can be specified based on intracranial recordings directly from the hippocampus and rhinal cortex, which provide both the temporal and spatial resolution needed to unambiguously resolve this question. We used a continuous recognition paradigm in which words are presented sequentially on a computer screen and patients have to specify whether the word is presented for the first or second time. In a previous analysis of poststimulus effects, we found that successful memory formation was associated with increased hip-

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Correspondence should be addressed to Dr. Juergen Fell, Department of Epileptology, University of Bonn, Sigmund-Freud-Strasse 25, D-53105 Bonn, Germany. E-mail: juergen.fell@ukb.uni-bonn.de.

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pocampal gamma power, but decreased rhinal and hippocampal power in the beta and alpha range (Fell et al., 2008). In the present study, the following hypotheses were targeted. First, we wanted to clarify by direct EEG recordings from within the human MTL whether prestimulus theta band activity indeed predicts subsequent memory, as reported based on source reconstruction of MEG data (Guderian et al., 2009). Second, we asked whether prestimulus power changes in other frequency bands precede successful memory formation. Third, we wanted to assess whether prestimulus effects related to successful memory formation suggest an earlier initiation of memory-related activations similar to those occurring in the poststimulus interval, or whether they indicate specific preparatory processes.

## Materials and Methods

Intracranial EEG was recorded from 31 patients (14 female) suffering from pharmacoresistant temporal lobe epilepsies during a continuous word recognition experiment. Depth electrodes comprising 10 platinum contacts were implanted stereotactically along the longitudinal axis of each MTL (Van Roost et al., 1998) during presurgical evaluation because the seizure onset zone could not be precisely determined with noninvasive investigations. Presurgical evaluation revealed unilateral pathologies for all patients included in the present study. To reduce potential contamination by epileptogenic processes, only EEG recordings from the MTL contralateral to the zone of seizure origin were analyzed (Puce et al., 1989; Grunwald et al., 1995).

Patients ranged in age from 16 to 61 years (mean 40 years) and in duration of their epilepsy from 4 to 57 years (mean 23 years). At the time of the recordings, all patients received anticonvulsive medication (plasma levels within the therapeutic range). Magnetic resonance imaging (MRI) scans or postsurgical histological examinations demonstrated unilateral hippocampal sclerosis in 16 patients (left: 5; right: 11), unilateral extrahippocampal lesions without signs of hippocampal sclerosis in 9 patients (left: 3; right: 6), unilateral hippocampal sclerosis with additional extrahippocampal lesions on the same side in 3 patients (left: 2; right: 1), and no clear lesion in 3 patients. All but two patients underwent subsequent epilepsy surgery after implantation (17 selective amygdalohippocampectomies, 7 temporal two-thirds resections, 5 lesionectomies). Informed consent for the intracranial EEG recordings and the use of the data for research purposes was obtained by all patients. The study was approved by the ethics committee of the Medical Faculty of the University of Bonn.

For the continuous word-recognition paradigm, 300 frequent German nouns were selected (mean word frequency was 50 per 1 million words according to the CELEX lexical database, version 2.5); 150 stimuli were only presented once, whereas the other 150 words were shown with one repetition. This repetition occurred in 50% of the trials after a short lag of 3–6 words and in 50% after a long lag of 10–30 words. Thus, 450 words were presented consecutively with a duration of 300 ms per word. In temporal-lobe epilepsy patients memory abilities vary to a much larger degree than in healthy subjects (Helmstaedter, 2002). To ensure that the patients were neither overstrained nor bored by the task, the length of the interstimulus interval was adjusted to the subjects' abilities (assessed from the responses in a few pilot trials) and was either short (1600 ± 200 ms; $n = 6$), intermediate (2000 ± 200 ms; $n = 16$), or long (2700 ± 200 ms; $n = 9$). After each word, subjects had to indicate by pressing one of two buttons whether the word was new (left button) or whether it had already been presented before (right button).

Depth electroencephalograms were referenced to linked mastoids, bandpass-filtered [0.01 Hz (6 dB/octave) to 70 Hz (12 dB/octave)], and recorded with a sampling rate of 200 Hz. Electrode contact placement was ascertained by examining magnetic resonance images acquired in the sagittal, axial, and coronal planes and adjusted to the longitudinal axis of the hippocampus. Electrode contacts were localized based on the individual magnetic resonance images and comparison with standardized anatomical atlases (Duvernoy, 1988). In most cases, 2–3 electrodes were localized within the rhinal cortex and 4–6 electrodes within the hippocampus. The rhinal electrode was defined as the electrode located within the anterior parahippocampal gyrus (based on the MRI data) with the largest mean N400 amplitude (new words) between 200 and 600 ms (Grunwald et al., 1999). Because our methods cannot clearly separate perirhinal and entorhinal generators, we use the term rhinal cortex without intending to indicate an integrated rhinal processing stage. The hippocampal electrode was defined as the electrode located within the hippocampus (based on the MRI data) with the largest mean amplitude (old words) of a later positive component between 300 and 1500 ms (Fernández et al., 1999). EEG measures from right and left hemisphere were combined for statistical analyses, because lateralization of verbal memory in MTL epilepsy patients is variable due to functional shifts (Helmstaedter et al., 2006).

An automated artifact rejection was implemented using MATLAB 7.1 (MathWorks). For each segment, the SD of the data points as well as the SD of the gradients (the increase or decrease between two successive data points) were determined. A segment was rejected if any data point or gradient deviated >5 SDs from the mean. Thus, segments with abnormally high amplitudes as well as abrupt rises or falls were eliminated. On average, 17% of trials were removed based on these criteria. The data from four patients, which still exhibited artifacts (observed by visual inspection) after applying the automated rejection procedure, were in addition visually scanned for artifacts, and in total, 22 more trials were discarded. The average number of remembered trials was 79 (minimum: 26, maximum: 131), the average number of forgotten trials, 41 (minimum: 11, maximum: 109).

We analyzed the EEG responses to the first presentation of words shown with one repetition. Responses were classified as remembered or forgotten depending on whether the word was subsequently (i.e., at the second presentation) correctly identified or not. EEG responses were segmented from −1000 to 1400 ms with respect to stimulus onset and were filtered in the frequency range from 1 Hz to 49 Hz (1 Hz steps) by continuous wavelet transforms implementing Morlet wavelets with a bandwidth parameter $f_0/\sigma_f = 5$, i.e., roughly speaking, wavelets of five cycles length (Lachaux et al., 1999). Edge effects were minimized by concatenating mirrored (i.e., time inverted) segments at the left and right edge of the original segments, by performing the wavelet transforms on the extended segments, and by afterward discarding the concatenated parts. The concatenation of mirrored segments of the trial to the period preceding the trial may have two effects. (1) It reduces the temporal catchment area of the wavelet-transform (left wing), because no information from the time period before the selected window enters the wavelet-transform. This is a deliberate effect, because it reduces the influence of early poststimulus activity from the preceding trial. (2) It may occasionally induce the impression of broad-band high-frequency activity at the beginning of the trial due to a noncontinuous signal gradient. However, such a phenomenon was not observed in our data. To check whether the observed memory-related effects are affected by the mirroring procedure, we corroborated our analyses by cosine-tapered fast Fourier transforms requiring no mirroring (see supplemental material, available at www.jneurosci.org). Power values were averaged for nonoverlapping successive time windows of 100 ms duration from −1000 to 1400 ms (24 windows in total). Power values were normalized by dividing them by the average power across the complete 2.4 s interval separately for each subject and each filter frequency.

## Results

First, we investigated accuracy and reaction times as a function of subsequent memory for all new items. We found that 66.7 ± 21.3% of these items were remembered afterward. Performance did not differ between patients with left and right focal hemisphere ($t_{30} = 0.518$, $p = 0.61$) or between male and female patients ($t_{30} = 0.875$, $p = 0.39$). Classification of later-remembered items was slower than classification of later-forgotten items (886 ± 39 ms vs 834 ± 34 ms; $t_{31} = 4.08$; $p = 0.0003$). Next, we analyzed behavioral performance depending on whether items were correctly recognized as old (hits) or new (correct rejections), or whether they were incorrectly classified (misses and

false alarms). We found that 76.2 ± 30.7% (mean ± SD) of old and 66.6 ± 21.3% of new items, respectively, were classified correctly. Reaction times did not differ between hits and misses (878 ± 29 ms vs 880 ± 39 ms; n.s.), while they were faster for correct rejections than for false alarms (857 ± 36 ms vs 972 ± 42 ms; $p < 0.0001$; $t_{30} = 5.23$).

Figure 1*A* shows the differences due to memory (later remembered minus forgotten) of the normalized rhinal and hippocampal power changes. In the prestimulus domain, memory-related increases in the theta, alpha, and beta range between 1000 and 200 ms before stimulus onset can be observed. Specifically, the prestimulus effects seem to start in the theta range and then evolve across the alpha and beta range. For a first exploratory evaluation of prestimulus subsequent memory effects, we performed paired *t* tests (remembered vs forgotten) for each time/frequency element in the prestimulus domain (Fig. 1*B*). This analysis shows rhinal effects in the theta, alpha, lower beta, and upper beta range, as well as hippocampal effects in the theta and alpha range.

This evaluation was corroborated by a stringent nonparametric randomization test, implementing a cluster-based correction for multiple comparisons (Maris and Oostenveld, 2007) [alpha = 0.005, 10,000 randomizations] (Fig. 1*C*). Basically, this test compares cluster-based effects between two conditions (remembered, forgotten) with effects arising from data clusters, when trials have been randomly shuffled (trial-shuffled surrogates). Note that this procedure does not require multiple electrodes, but can be performed for single electrodes, deriving the clusters across the time and frequency dimensions. Next, six power measures were extracted based on these analyses (Table 1). All six measures yielded statistically significant differences due to memory on at least a 1% level. Rhinal theta and alpha power enhancement even survived rigorous Bonferroni correction (i.e., dividing the *p* value by the individual number of time/frequency elements and multiplying with 500, the total number of comparisons).

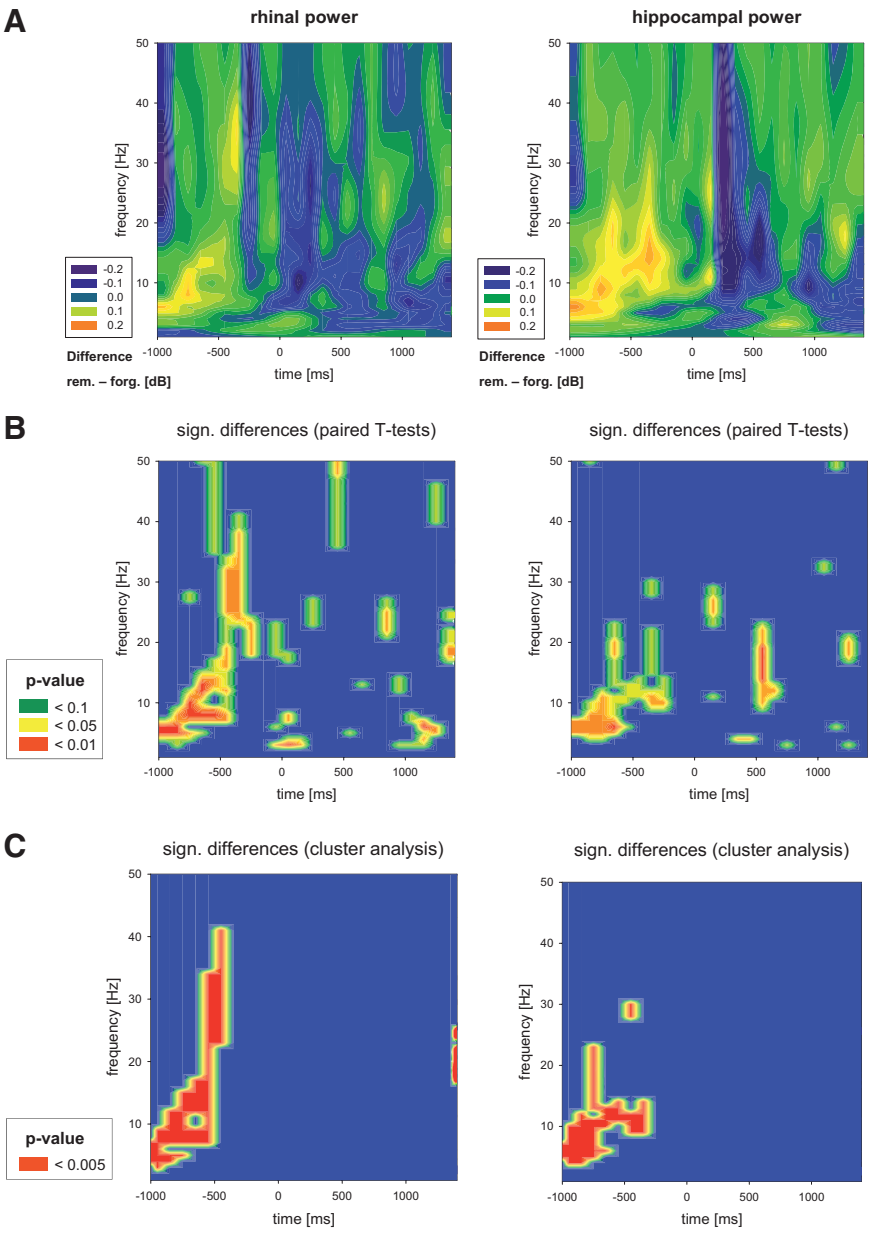


**Figure 1.** Difference plots for subsequently remembered versus forgotten words. ***A***, Normalized power. ***B***, *p* values resulting from paired *t* tests. ***C***, *p* values resulting from a cluster-based analysis.

We furthermore performed parametric discriminant analyses using pooled covariance matrices (SAS procedure DISCRIM; see also Table 1). The lowest error rate (32.26%) for predicting subsequent memory was reached for rhinal alpha power. A stepwise discriminant analysis with a significance level of $p = 0.1$ for entering and staying in the model revealed rhinal alpha power and hippocampal theta power as best predictors for later subsequent memory. Prediction based on both measures yielded an error rate of 27.42%. Finally, the time courses of rhinal alpha and hippocampal theta power show enhancements for subsequently remembered versus forgotten words during the prestimulus interval, followed by the inverse pattern in the early poststimulus interval (Fig. 2). The memory-related poststimulus differences for rhinal theta activity (200–400 ms; remembered vs forgotten: 0.97 ± 0.03 vs 0.97 ± 0.04, $p = 0.98$), rhinal alpha activity (100–200 ms; 1.07 ± 0.04 vs 1.21 ± 0.11, $p = 0.24$), and hippocampal alpha activity (100–200 ms; 1.05 ± 0.04 vs 1.10 ± 0.11, $p = 0.61$) are statistically not significant (paired *t* tests). There is a trend for a reduction of poststimulus hippocampal theta activity (200–400 ms; 0.96 ± 0.03 vs 1.04 ± 0.05, $p = 0.107$). However, two-way ANOVAs with prepost [prestimulus intervals: rhinal cortex (RH) −800, −400 ms, hippocampus (HI) −1000, −600 ms; poststimulus intervals: RH 100, 200 ms, HI 200, 400 ms] and subsequent memory as repeated measures revealed a trend for a rhinal alpha prepost* memory interaction ($F_{(1,30)} = 3.559$, $p = 0.069$), as well as a significant hippocampal theta prepost*memory interaction ($F_{(1,30)} = 6.437$, $p = 0.017$). Moreover, prestimulus and poststimulus differences due to memory were interindividually

**Table 1. Subsequent memory effects for six prestimulus EEG measures as revealed by paired *t* test and linear discriminant analyses**

| Measure (iEEG power) | Time range [ms] | Frequency range [Hz] | *p* value (paired *t* test) | Bonferroni corrected | Error rate (discriminant analysis) |
|---|---|---|---|---|---|
| RH: theta | −1000; −700 | 4–7 | 0.00075 | 0.031 | 37.10% |
| RH: alpha | −800; −400 | 8–12 | 0.0014 | 0.036 | 32.26% |
| RH: beta1 | −700; −400 | 13–17 | 0.0097 | n.s. | 38.71% |
| RH: beta2 | −500; −300 | 23–34 | 0.0081 | n.s. | 40.32% |
| HI: theta | −1000; −600 | 3–7 | 0.0080 | n.s. | 38.71% |
| HI: alpha | −900; −200 | 8–12 | 0.0092 | n.s. | 37.10% |

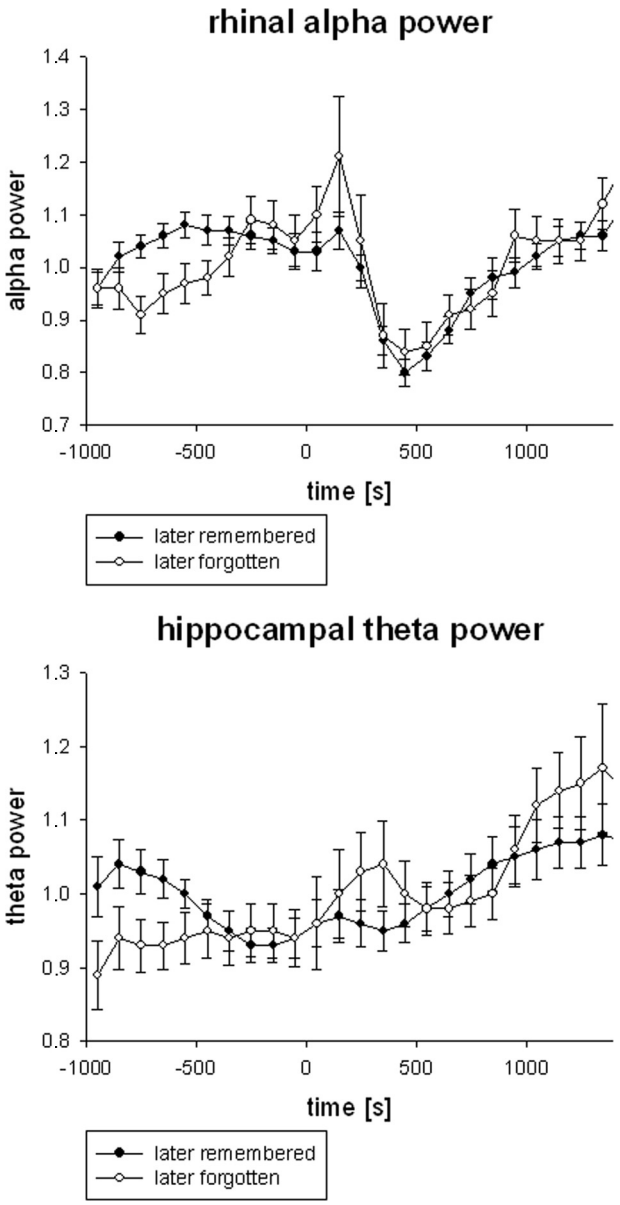


**Figure 2.** Time courses for normalized rhinal alpha power and hippocampal theta power.

negatively correlated (rhinal alpha: $r = -0.436$, $p < 0.01$; hippocampal theta: $r = -0.452$, $p < 0.01$; supplemental Fig. 2, available at www.jneurosci.org as supplemental material, shows the corresponding scatterplots).

Finally, we investigated whether the memory-related differences for the rhinal and hippocampal power measures were interindividually correlated within the prestimulus and poststimulus time range. For the prestimulus range, we found statistically significant correlations between rhinal theta and alpha power ($r = 0.418$; $p < 0.01$), rhinal alpha and beta power ($r = 0.725$; $p < 10^{-5}$), and hippocampal theta and alpha power ($r = 0.574$; $p < 0.001$). For the poststimulus time range, we again detected statistically significant correlations between rhinal theta and alpha power ($r = 0.638$, $p < 0.0001$) and hippocampal theta and alpha power ($r = 0.662$, $p < 0.0001$).

## Discussion

Based on intracranial EEG recordings we detected an enhancement of prestimulus theta- and alpha-band activity in the rhinal cortex and hippocampus, which predicted successful memory formation. Within the rhinal cortex, but not within hippocampus, the prestimulus effects moreover extended into the beta range up to 34 Hz. Through additional statistical analyses (see supplemental material, available at www.jneurosci.org), we validated that these findings do not depend on the different interstimulus intervals and are not caused by serial behavioral effects. We furthermore evaluated whether prestimulus theta and alpha power effects are correlated with poststimulus phase-locking effects (Fell et al., 2008), as well as whether prestimulus slow shifts predicted subsequent memory (Otten et al., 2006). These analyses revealed no statistically significant results (see supplemental material, available at www.jneurosci.org).

Recent microelectrode recordings in epilepsy patients—which allow the simultaneous investigation of oscillations in local field potentials and action potentials—explored the functional relevance of neural oscillations for memory processes. Jacobs et al. (2007) were the first to report that action potentials within the human medial temporal lobe are locked to specific phases of oscillations in different frequency bands, suggesting that these oscillations serve as an internal clock for the timing of action potentials. Mechanistically, this coupling may be related to the fact that, in particular, high-frequency oscillations are controlled by inhibitory interneurons which leave only brief windows for excitation of pyramidal cells (Cardin et al., 2009). Furthermore, Rutishauser et al. (2010) recently found that the magnitude of hippocampal spike-field coherence predicted memory performance in a recognition memory task. Together, these findings indicate that oscillations within the medial temporal lobe are critical for successful information encoding.

In our data, the memory-related increase of prestimulus theta power is in accordance to the well known relevance of hippocampal theta activity for memory processes (Kahana et al., 2001) and is consistent with the findings of a recent MEG study (Guderian et al., 2009). In that study, memory-related theta differences became significant very shortly before stimulus presentation (starting at ~−200 ms). In our experiment, we observed a memory-related theta increase starting as early as 1000 ms before word presentation, accompanied by a successive alpha power enhancement. Importantly, the precise time point of word presentation was unknown to participants in our study (jittered intertrial interval), but was precisely defined (500 ms after presentation of a fixation cross) in the study by Guderian et al.

(2009), which may contribute to the different time courses of theta power. Moreover, peristimulus theta time courses reported by Guderian et al. (2009) were calculated based on a wavelet with a center frequency of 7 Hz, which may have included some of the activity we define as alpha.

Similar to the MEG results by Guderian et al. (2009), we observed an inverse pattern of memory-related theta activity shortly after stimulus presentation compared with activity before the stimulus and a negative correlation of prestimulus and poststimulus memory-related effects (see also supplemental Fig. 2, available at www.jneurosci.org as supplemental material). There is a trend for a memory-related reduction of poststimulus hippocampal theta activity in the time range between 200 ms and 400 ms after stimulus presentation. In a previous study (Fell et al., 2008), we interpreted the tendency (although statistically not significant) of a memory-related broad-band power decrease in the early poststimulus time range as reflecting the shutdown of ongoing neural activity to prepare for incoming stimulus information. A memory-related poststimulus reduction of hippocampal theta activity has also been reported by Sederberg et al. (2007). Our data thus indicate that the prestimulus effects are not related to an earlier initiation of memory-related activations, but that they reflect specific preparatory processes. Because stimulus-triggered hippocampal theta activity has been found to be particularly related to memory retrieval (Klimesch et al., 2001; Guderian and Düzel, 2005; Osipova et al., 2006), Guderian et al. (2009) speculated that the prestimulus theta increase my reflect the activation of a mnemonic context, in which the subsequently presented item can be embedded. This contextual information, for instance, could consist of the word category, the expected position of the word on the computer screen, its luminance, or its timing. Applying a method suitable to detect directional coupling (Rosenblum and Pikovsky, 2001; Axmacher et al., 2008; Wagner et al., 2010), we indeed found evidence for an increased hippocampal*rhinal interaction for subsequently remembered compared with forgotten items in the prestimulus time range, which may be interpreted as a sign of memory retrieval (see supplemental material, available at www.jneurosci.org). Our data furthermore indicate that the prestimulus theta increase may initiate the subsequent alpha enhancement, because both effects are interindividually correlated.

But how can the memory-related prestimulus alpha increase, itself, be interpreted? Several recent studies indicate that the alpha rhythm is not just related to cortical idling or to inwardly versus outwardly directed attention (Ray and Cole, 1985). Instead, alpha activity seems to reflect inhibitory top-down control, which may prepare for optimal subsequent task processing and executive functioning (Cooper et al., 2003; Klimesch et al., 2007; Min and Herrmann, 2007). For instance, alpha power was found to be increased in "dorsal-stream" areas devoted to processing of spatial relations during working memory maintenance of a face identity but not during maintenance of a face direction, suggesting an active role of alpha in the inhibition of task-irrelevant areas (Jokisch and Jensen, 2007). Furthermore, a rhinal and hippocampal alpha rhythm (between 10 and 12 Hz) has been detected in rats, which was prominent in a familiar environment, but disappeared in a novel environment (Nerad and Bilkey, 2005). This result is consistent with the idea of an alpha-related inhibitory control of memory formation, because there is no need for fresh encoding of the familiar environment. Based on these findings, we suggest that the observed memory-related prestimulus rhinal and hippocampal alpha increase may reflect an inhibitory top-down mechanism, which prepares for stimulus-triggered memory processing.

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