

COGNITIVE NEUROSCIENCE

Electrophysiological signature of working and long-term memory interaction in the human hippocampus

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Abstract

Recent findings indicate that the hippocampus is not only crucial for long-term memory (LTM) encoding, but plays a role for working memory (WM) as well. In particular, it has been shown that the hippocampus is important for WM maintenance of multiple items or associations between item features. Previous studies using intracranial electroencephalography recordings from the hippocampus of patients with epilepsy revealed slow positive potentials during maintenance of a single item and during LTM encoding, but slow negative potentials during maintenance of multiple items. These findings predict that WM maintenance of multiple items interferes with LTM encoding, because these two processes are associated with slow potentials of opposing polarities in the hippocampus. Here, we tested this idea in a dual-task paradigm involving a LTM encoding task nested into a WM Sternberg task with either a low (one item) or a high (three items) memory load. In the high WM load condition, LTM encoding was significantly impoverished, and slow hippocampal potentials were more negative than in the low WM load condition. Time-frequency analysis revealed that a reduction of slow hippocampal activity in the delta frequency range supported LTM formation in the low load condition, but not during high WM load. Together, these findings indicate that multi-item WM and LTM encoding interfere within the hippocampus.

Introduction

Traditionally, the medial temporal lobe (MTL) has been considered necessary for long-term memory (LTM) encoding, but not for short-term maintenance of items in working memory (WM), because patients with medial temporal lesions are not impaired in simple WM tasks involving maintenance of single items (Cave & Squire, 1992). However, recent findings indicate that the MTL does play a role in WM processes if multiple items or conjunctions of item features are involved (Hannula *et al.*, 2006; Olson *et al.*, 2006; Piekema *et al.*, 2006). In a recent study using intracranial electroencephalography (iEEG) recordings in the hippocampus of presurgical epilepsy patients, we observed slow direct current (DC) potentials with a positive slope during WM maintenance of a single item, and increasingly negative potentials during maintenance of multiple items (Axmacher *et al.*, 2007). Negative DC potentials were associated with an overall increase of activity, most notably in the gamma frequency range, consistent with findings from the neocortex (e.g. Speckmann & Elger, 1999). Slow potentials probably correspond to sustained modifications of firing rate, which are necessary to maintain stimulus information during WM (Suzuki *et al.*, 1997; Young *et al.*, 1997; Khader *et al.*, 2007). However, similar potentials were observed during LTM encoding as well: iEEG recordings during a word-list learning task revealed late hippocampal potentials with a time course similar to the

slow WM-related potentials, which were significantly more positive for items that were subsequently recalled as opposed to forgotten items (Fernandez *et al.*, 1999). Taken together, slow hippocampal positive potentials were found during maintenance of a single item in WM and during LTM encoding, whereas negative potentials were observed during multi-item WM.

These results question a double dissociation of the brain regions underlying WM and LTM (Ranganath & Blumenfeld, 2005) and may explain why WM maintenance of a single item supports LTM encoding of this item (Schon *et al.*, 2004; Ranganath *et al.*, 2005), because both processes are associated with positive slow hippocampal potentials. However, they also predict that maintenance of multiple items should interfere with simultaneous LTM encoding of other items. More generally, it could be argued that WM processes that rely on the hippocampus, such as those involving multiple items or associations between item features, are likely to interfere with LTM encoding of unrelated information in the same region. The shared neural processes underlying WM and LTM actually suggest that they rely on a common neural basis, as proposed by theories arguing that WM relies on attentional processing of current stimuli or LTM contents (Fuster, 1995; Cowan, 1999).

Here, we tested these predictions by using a dual-task paradigm in which subjects encoded novel faces into LTM while simultaneously maintaining either a single or multiple different items in WM. This design was similar to a previous study on the interaction of WM load with directed attention (De Fockert *et al.*, 2001), which revealed that a high WM load impaired selective attention. However, no previous

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electrophysiological study directly tested the effect of WM load on LTM encoding of other items.

Materials and methods

Subjects

Six epilepsy patients (three women; mean age \pm SD 47.1 \pm 7.0 years) participated in the iEEG study. All patients showed a unilateral ictal onset zone; in five patients, unilateral hippocampal sclerosis was confirmed histologically. Only patients who were able to conduct this relatively demanding task after an exploratory test session were included ($>$ 75% correct responses in the low WM load condition). Recordings were performed at the Department of Epileptology, University of Bonn, Germany, from 2006 to 2007. No seizure occurred within 24 h before the experiment. Only data from the hemisphere contralateral to the seizure onset zone were included in the analysis. The study was in accordance with the 2008 revision of the Declaration of Helsinki, and was approved by the ethics committee of the Medical Faculty, University of Bonn, and all subjects gave written informed consent.

Experimental paradigm

We used a dual-task experiment to manipulate WM load during simultaneous LTM encoding. An overview of the paradigm is depicted in Fig. 1. To create a sufficient WM load, we used a serial version of the Sternberg item recognition test (Sternberg, 1975) in which three abstract symbols were consecutively presented at the beginning of each trial. At the end of each trial, subjects had to decide whether a sequence of symbols matched the symbols presented previously. WM load was either high (with three different symbols), or low (two 'default' symbols plus one trial-unique symbol). Visual features were thus similar in the two conditions. Both tasks were designed to produce both sufficient memory load and demanding task difficulty (e.g. Eng *et al.*, 2005), without overstraining the subjects' abilities, especially considering the high individual differences in WM capacities and interference susceptibility (Mecklinger *et al.*, 2003). Because recent studies have suggested a stronger MTL involvement in WM for complex and trial-unique stimuli (Hasselmo & Stern, 2006), the symbols were generated using the Windows font 'Wingdings' (Microsoft Office 2003; Microsoft Corp., Seattle, WA, USA) to create trial-unique sequences of stimuli rather than using simple, highly familiar stimuli such as letters or numbers. During the maintenance

phase of the WM task, subjects were presented with black-and-white photographs of unknown male or female faces (100 male and 100 female faces in total) in each trial. The faces were previously rated by a large independent group of subjects as neutral with respect to facial expression. To guarantee attentive processing of the faces, subjects were asked to perform a simple sex-discrimination task during face presentation. Subjects were instructed that both the Sternberg and the sex-discrimination task were equally important, and that a recognition phase would follow after each of the four encoding blocks. Only trials with correct responses in both the Sternberg and the sex discrimination task were used for the iEEG analyses. In order not to exceed the participants' abilities, the study was conducted in four consecutive blocks, each comprising an encoding and a retrieval part. Therefore, subjects inevitably knew that a memory retrieval for the face stimuli would follow during encoding in the second block; to ensure equal conditions in all blocks, subjects were explicitly instructed that a recognition memory test for the faces (and only for the faces) would follow after encoding.

Encoding phase

Subjects completed a total of 200 trials. These trials were subdivided into four runs of 50 trials each to ascertain a stable level of attention during the entire length of the paradigm. Trials were administered in a randomized, counterbalanced order across subjects. Trials began with a fixation cross (2000 ms), followed by three sequentially presented WM stimuli (1000 ms each), each separated by a fixation cross for 500 ms. Stimulus presentation in the WM task was followed by a pause of 1000–1250 ms during which a fixation cross was shown, before the LTM face stimulus was presented for 1000 ms. After another pause of 1500–2000 ms, the WM retrieval probe was presented for 3000 ms. Stimuli were presented on a laptop screen at about 50 cm distance from the patients.

Recognition phase

Participants were given a recognition memory test 3 min following each of the four encoding blocks to assess recognition memory of all 200 previously shown faces, plus 100 novel faces. During recognition, participants were shown each face individually on a computer screen and were instructed to judge, on a scale from 1 to 4, whether each face was presented during the scanning session (1: sure old; 2: unsure old; 3: unsure new; 4: sure new). Presentation was self-paced, i.e. each stimulus was presented until subjects gave a response.

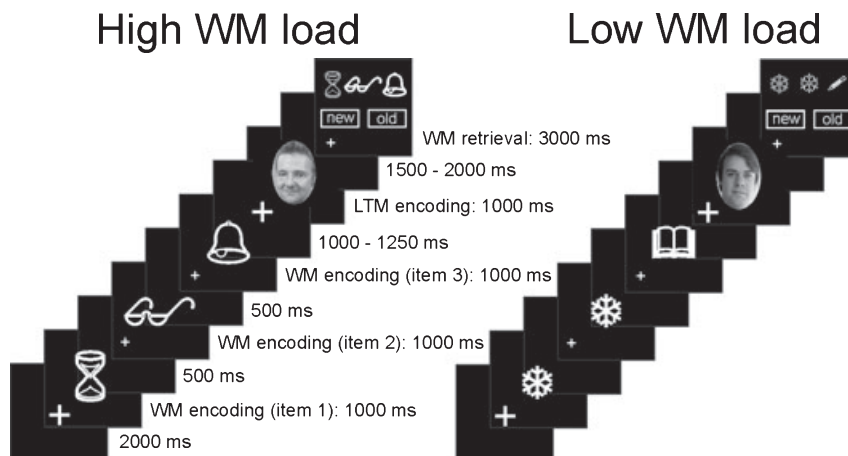


FIG. 1. Overview of the paradigm. Left: high WM load condition. A series of three different items was presented sequentially in a Sternberg paradigm. During the maintenance phase, a face stimulus was shown which was encoded into LTM. Right: in the low WM load condition, only a single item was maintained in WM.

Recordings and analyses

Multi-contact depth electrodes were inserted for diagnostic purposes using a computed tomography-based stereotactic insertion technique (Van Roost *et al.*, 1998). The location of electrode contacts was ascertained by post-implantation magnetic resonance imaging (MRI) in each patient. Depth EEG was referenced to linked mastoids, recorded at a sampling rate of 1000 Hz, and band-pass filtered [0.01 Hz (6 dB/octave) to 300 Hz (12 dB/octave)]. Artefacts were visually rejected, and only trials without artefacts were taken into account for further behavioural and EEG analysis. Thus, $59.7 \pm 21.4\%$ (mean \pm SD) of all trials were rejected. We averaged data across all hippocampal contacts from the contralateral (non-focal) depth electrode in each patient, which avoids any selection bias. Patients had 3.83 ± 1.84 (mean \pm SD) contacts (range 1–6) within the hippocampus. We analysed late potentials in the hippocampus, which were previously observed during both LTM formation (Fernandez *et al.*, 1999) and WM processes (Axmacher *et al.*, 2007). These potentials were calculated as the average voltage across a time window between 500 and 1200 ms (averaged across trials and electrodes), triggered to the onset of the face stimuli, which were to be encoded into LTM. We chose this analysis window by visual inspection of the potentials averaged across experimental conditions. In general, we have found that the duration of memory-related effects in the hippocampus tends to differ according to the exact experimental design; for example, subsequent memory effects from 500 to 2000 ms were observed in a word-list learning task with free recall (Fernandez *et al.*, 1999), between 400 and 900 ms in a continuous recognition paradigm (Fell *et al.*, 2008), and between 1000 and 2000 ms during WM maintenance (Axmacher *et al.*, 2007). Baseline correction was performed using a baseline between -200 and 0 ms before onset of face stimuli. Data were analysed using the BRAIN VISION ANALYZER software (Brain Products, Munich, Germany) as well as with MATLAB.

Frequency-specific amplitude values were calculated by convolving the signal with a complex Morlet wavelet and extracting the absolute values of the convolved signal in the frequency range from 1 to 100 Hz (1-Hz steps). For statistical analyses, amplitude values (i.e. $\sqrt{[\text{real}(c)^2 + \text{imag}(c)^2]}$ if c are the complex wavelet coefficients) were averaged for non-overlapping successive time windows of 500-ms duration from 0 to 1500 ms after the onset of the face stimulus. For graphical depiction and statistical analyses, amplitude values were normalized to the prestimulus time window (baseline -200 to 0 ms) and then transformed into dB scale ($10 \cdot \log_{10}$). It should be noted that the choice of a baseline period is inherently difficult in rapidly timed experiments. With the selected baseline, we cannot exclude contamination with post-stimulus activity, especially in the lower frequency range. However, if anything this would decrease the effects observed in our study; the actual differences may thus be even more pronounced. Moreover, selection of a longer baseline period would impose even more severe problems, because presentation of the face stimuli was preceded by the maintenance phase of the Sternberg experiment, which contains load-dependent activity itself. A longer baseline period would increase the impact of this activity. Due to the intrinsic logarithmic frequency scaling of the wavelet decomposition, higher frequencies are not statistically independent if sampled too closely on an equidistant frequency scale. Therefore, the EEG was analysed in the following spectral bands: δ_{1_1} : 1–2 Hz; δ_{2_1} : 3–4 Hz; θ_{1_1} : 5–6 Hz; θ_{2_1} : 7–8 Hz; α_{1_1} : 9–10 Hz; α_{2_1} : 11–12 Hz; β : 13–30 Hz; γ : 31–100 Hz. In analyses of variance (ANOVAs) of the amplitude values, only effects of or interactions with the factors ‘load’ and ‘memory’ are reported. To avoid low numbers of trials, items rated as ‘sure old’ and ‘unsure old’ were collectively labelled

‘remembered’, and items rated as ‘sure new’ and ‘unsure new’ were collectively labelled ‘forgotten’ in all analyses. Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA), and degrees of freedom in the ANOVAs were Huynh–Feldt-corrected for inhomogeneities of covariance when necessary (Huynh & Feldt, 1976). Mean values below are shown \pm SD.

Results

Behavioural data

Performance in the Sternberg task was significantly better in the low than the the high WM load condition (92.3 ± 3.7 vs. $78.5 \pm 5.9\%$; $t_5 = 3.20$; $P < 0.05$). Accuracy in the sex discrimination task tended to be higher in the low load condition (low load: $63.5 \pm 23.0\%$; high load: $60.3 \pm 25.0\%$; $t_5 = 2.22$; $P = 0.08$), while reaction times did not differ (low load: 897 ± 76 ms; high load: 896 ± 76 ms; $t_5 = 0.14$; $P = 0.89$). Receiver-operating characteristics in the high and low load condition are shown in Fig. 2. The proportion of remembered items was significantly higher in the ‘low load’ condition than the ‘high load’ condition (46.5 ± 8.5 vs. $35.9 \pm 9.0\%$; $t_5 = 3.51$; $P < 0.05$); of the new items, $34.3 \pm 2.9\%$ were incorrectly considered old (false alarms). Thus, consistent with our hypothesis, LTM encoding was indeed significantly impaired during WM maintenance of multiple items as compared with a single item. To test whether performance was better than chance, we compared the hit rates in the low and high load condition with the rate of false alarms. For the low load condition, hit rate was significantly higher than the rate of false alarms, both if only ‘sure old’ responses were considered ($t_5 = 2.85$; $P < 0.05$) and if ‘sure old’ and ‘unsure old’ responses were pooled ($t_5 = 3.04$; $P < 0.05$). For the high load condition, this comparison was only significant for the comparison of ‘sure old’ responses ($t_5 = 2.10$; $P < 0.05$), but not if all ‘old’ responses were pooled ($t_5 = 1.02$; $P = 0.18$). Four patients showed a higher number of ‘old’ responses in the high load condition as compared with the false alarm rate (corresponding to positive d' -values; see Table 1). For the analyses of iEEG data, we thus present both results from the entire group and from the subset of four subjects with significant recognition memory in the high load condition (subjects 1–4 in Table 1).

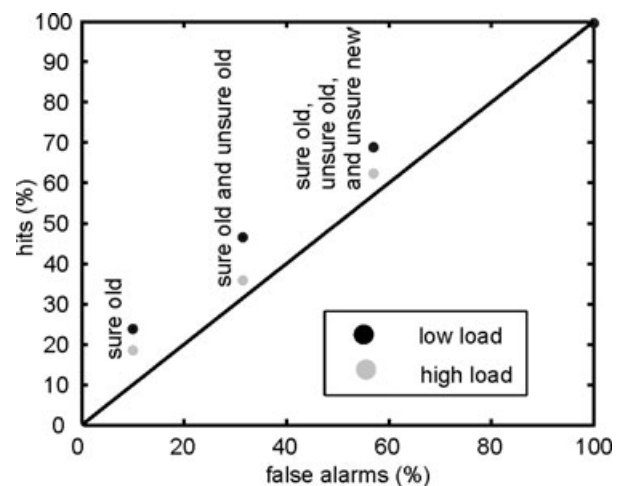


FIG. 2. Behavioural results. Receiver-operating characteristics in the two conditions, i.e. ratio of hits and false alarms according to the different response criteria (based on a four-step response).

TABLE 1. Average recognition memory scores in all patients

Subject	d' values*			
	Low load		High load	
	Sure	Sure and unsure	Sure	Sure and unsure
1	1.03	0.85	0.88	0.60
2	0.79	0.40	0.61	0.05
3	0.65	0.66	0.20	0.16
4	2.96	0.42	2.70	0.19
5	0.23	-0.05	0.18	-0.05
6	0.65	0.33	0.37	-0.37

*Results are given as d' values for items presented in the low and high load condition for all six patients.

Intracranial EEG data

First, we calculated event-related potentials (ERPs) in the hippocampus. Because slow potentials were previously observed as the neural signature underlying WM maintenance in the hippocampus (Axmacher *et al.*, 2007), we investigated late potentials averaged across all hippocampal electrodes in a window between 500 and 1200 ms. Figure 3 depicts ERPs in each individual patient as well as the grand average across patients. In the high WM load condition, traces were more negative than in the low WM load condition, most visibly in the grand average. To quantify this effect, we calculated a two-way ANOVA with 'memory' and 'load' as repeated measures. This analysis revealed a significant effect of 'load' ($F_{1,5} = 9.543$; $P < 0.05$), but no effect of 'memory' and no interaction. Only a very small number of trials was rated as 'sure old', especially in the high load condition (low load: 10.7 ± 8.9 ; high load: 6.2 ± 5.3); only one patient had more than ten trials in both conditions. However, when we analysed only data from the four patients in whom the pooled number of 'sure old' and 'unsure old' responses in the high load condition was greater than the number of false alarms (also pooled across 'sure old' and 'unsure old' responses) (patients 1–4 in Table 1), the results were qualitatively similar to the findings of the entire group (Supporting information, Fig. S1). Statistically, we conducted an ANOVA on the group of four subjects showing above chance memory performance; however, the effect of 'memory load' did not reach significance in this subgroup ($P = 0.125$). To test whether this lack of a significant effect is due to the small number of subjects, we used a jackknife procedure in which we calculated the same ANOVA for all 15 possible combinations of four subjects. The value we obtained if we excluded the two subjects with low memory performance was very similar to the P -values of the entire group, i.e. the P -value was within the range defined by the 25% and the 75% quantiles around the median P -value of the entire group (median; 25 and 75% quantiles: 0.115; 0.028; 0.133). In other words, the P -value for the effect of 'memory load' in the group of four subjects with above-chance memory performance was within the range that could be expected for such a small group. Furthermore, we tested whether the values from the group of four subjects differed from the means of the entire group of six subjects by performing t -tests for the four conditions (i.e. 'high load remembered', 'high load forgotten', 'low load remembered' and 'low load forgotten'). We found that none of these tests reached significance. Although lack of an effect does not exclude a difference due to the low statistical power, these tests further suggest that the results from the subgroup of four subjects resemble the findings from the entire group of six subjects.

Next, we analysed the effects of memory load and encoding success on the amplitudes of oscillatory activity. Figure 4 shows grand averages of time–frequency (wavelet) transforms. Individual time–

frequency plots of subsequent memory effects in each patient are presented in supporting Fig. S2. A four-way ANOVA with 'memory', 'load', 'band' and 'time window' as repeated measures revealed a significant four-way interaction ($F_{14,70} = 2.201$; $P < 0.05$; $\epsilon = 0.568$) and a significant 'load' \times 'time' interaction ($F_{2,10} = 12.099$; $P < 0.05$; $\epsilon = 0.565$). We thus analysed effects in the different bands separately. In the δ_1 band, there was a significant three-way interaction ($F_{2,10} = 23.049$; $P < 0.01$; $\epsilon = 0.638$) and a significant 'load' \times 'memory' interaction ($F_{1,5} = 9.022$; $P < 0.05$). No significant effects including the factors 'load' or 'memory' were found in any other band. Average δ_1 amplitudes in the different conditions are depicted in Fig. 4C, and mean values of each patient are shown in Fig. 4D (all values averaged across the entire time range from 0 to 1500 ms). In the low load condition, mean δ_1 amplitudes were reduced for subsequently remembered items in all six patients. In the high load condition, δ_1 amplitudes increased for subsequently remembered items in five patients but decreased in one patient.

We compared the four WM load/LTM conditions in the δ_1 frequency range using the *post-hoc* Scheffé test. δ_1 amplitude for subsequently remembered and forgotten items differed significantly in the low load condition ($P < 0.05$), where subsequently remembered items were associated with a reduction of δ_1 amplitude, but not in the high load condition. Furthermore, subsequently remembered items in the high load condition elicited significantly enhanced δ_1 amplitude as compared with subsequently remembered items in the low load condition ($P < 0.05$).

Again, effects were qualitatively identical when we analysed only data from the four patients in which the pooled number of 'sure old' and 'unsure old' responses in the high load condition was greater than the number of false alarms (supporting Fig. S1). We also repeated the statistical analysis for the δ_1 band amplitude with the reduced group of four subjects. Consistent with the results from the entire group, a three-way ANOVA with the repeated measures 'load', 'memory' and 'time' revealed a significant three-way interaction ($F_{2,6} = 25.968$; $P < 0.01$; $\epsilon = 0.705$) and a significant 'load' \times 'memory' interaction ($F_{1,3} = 32.605$; $P < 0.05$). Again, *post-hoc* Scheffé tests indicated that δ_1 amplitude for subsequently remembered and forgotten items differed significantly in the low load condition ($P < 0.05$), where subsequently remembered items were associated with a reduction of δ_1 amplitude, but not in the high load condition. Subsequently remembered items in the high load condition elicited significantly enhanced δ_1 amplitude compared with subsequently remembered items in the low load condition ($P < 0.05$).

These effects indicate that in the low load condition, memory formation is associated with reduced δ_1 amplitude, and that an increased WM load is associated with enhanced δ_1 amplitude for subsequently remembered items. Next, we investigated whether this load effect on δ_1 amplitude is directly related to the impaired memory in the high WM load condition. Thus, we computed the correlation between the difference in δ_1 amplitude as a function of memory load (i.e. δ_1 amplitude for remembered items in the high load condition minus δ_1 amplitude for remembered items in the low load condition) vs. the load effect on recognition memory (i.e. the difference in the percentage of remembered items in the high and low load condition). The results are depicted in Fig. 4E. Despite the small sample size, we observed a trend for a correlation in the expected direction: subjects with a higher load effect on δ_1 amplitude were also more impaired in recognition memory as a function of the increased WM load ($R = 0.79$; $t_5 = 1.95$; $P < 0.1$).

A number of studies indicate that long-term recognition memory with high confidence can remain relatively intact after bilateral

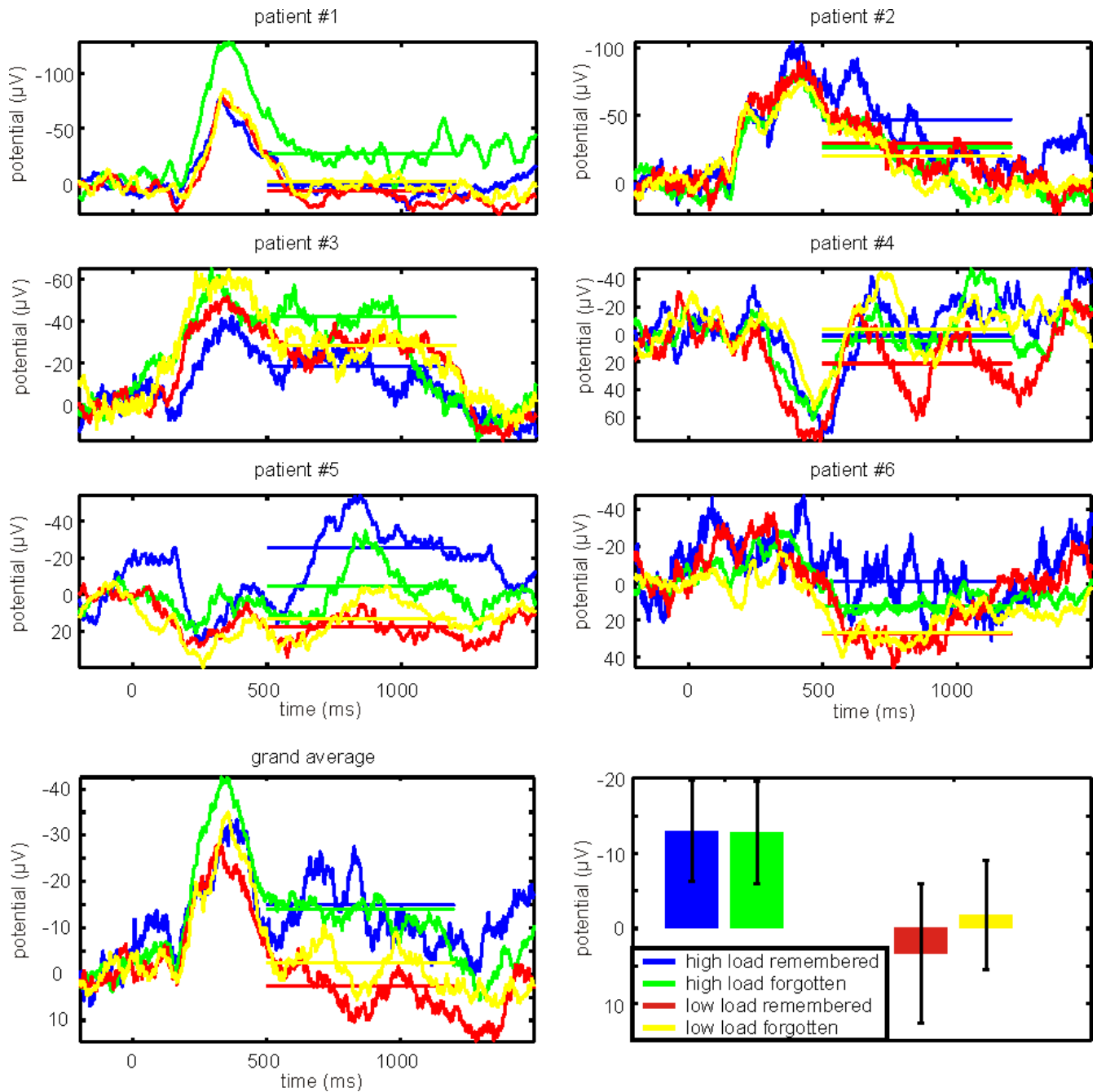


FIG. 3. Averaged ERPs in the hippocampus. ERPs averaged across all hippocampal contacts are shown both for each subject and averaged across subjects (bottom); events are triggered to the onset of the face stimulus which was to be encoded into LTM. The lines indicate averaged slow potentials between 500 and 1200 ms. Potentials were significantly more negative in the high load than in the low load condition. Error bars depict SEM across subjects.

hippocampal injury, but is impaired after rhinal injury (for recent studies, see Bowles *et al.*, 2007; Vann *et al.*, 2009). This might suggest that the interference between WM load and recognition memory as observed in our data does not emerge in the hippocampus, but that the locus of WM–LTM interference may be in the rhinal cortex. We tested this hypothesis in five of the six patients who had electrodes implanted in the rhinal cortex in addition to the hippocampus. The results are shown in Figs 5 (ERPs) and 6 (time–frequency data). No load effect on ERPs occurred in the rhinal cortex, and the same ANOVA of time–frequency data as conducted for the hippocampus did not reveal any effect of or interaction with the factors ‘load’ or ‘memory’ (all $P > 0.2$). These results strongly suggest that the

observed effects in the hippocampus are not transferred from the rhinal cortex into the hippocampus.

In summary, WM load induced more negative late hippocampal ERP components, and hippocampal δ_1 band activity decreased for subsequently remembered as compared with forgotten items in the ‘low load’ and increased with WM load for remembered items.

Discussion

Using a dual-task paradigm in which a stimulus was encoded into LTM during maintenance of either a single or multiple items in WM, we found evidence for an interference of multi-item WM with LTM

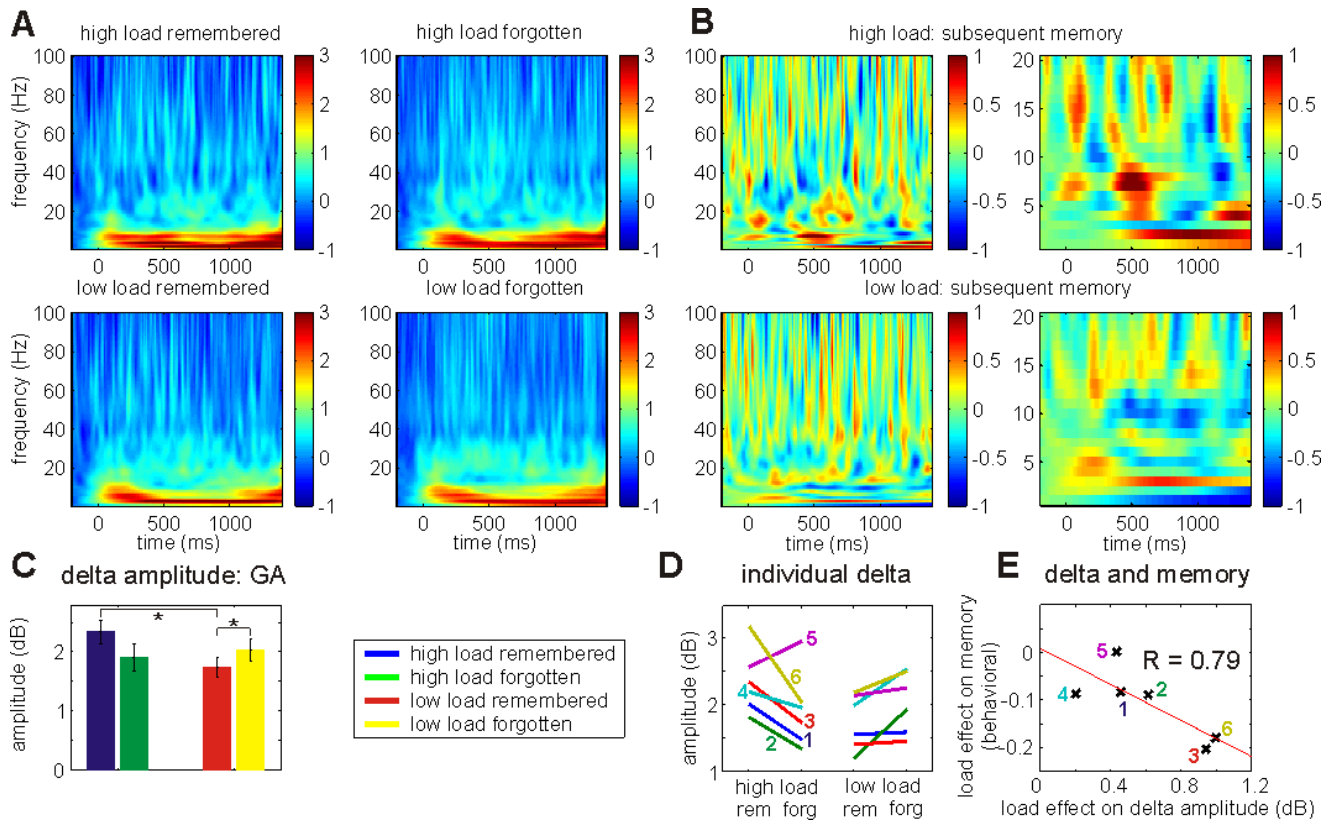


FIG. 4. Hippocampal δ_1 band activity is associated with WM–LTM interference. (A) Amplitude (dB relative to baseline) extracted by wavelet decompositions in the different conditions. (B) Subsequent memory effects (i.e. remembered vs. forgotten items) both for all frequency values (left) and specifically in the lower frequency range between 1 and 20 Hz. In the high load condition, δ_1 amplitude was enhanced for subsequently remembered items, whereas it decreased with LTM encoding in the low load condition. (C) δ_1 band amplitude (1–2 Hz; averaged across the entire time range between 0 and 1500 ms) in the different conditions. (D) δ_1 band amplitude for each subject. (E) Correlation of load-dependent changes of δ_1 band amplitude (recognized items, high vs. low load condition) with load effects on recognition memory (difference in the proportion of recognized items in the high vs. low load condition). Numbers in D and E indicate individual subjects. Error bars depict SEM across subjects. * $P < 0.05$.

encoding in the hippocampus: LTM encoding was significantly impaired during maintenance of multiple items, which was associated with negative slow potentials in the hippocampus. A reduction of hippocampal δ_1 band activity predicted LTM formation in the low WM load condition, and δ_1 amplitude increased with WM load for remembered items.

Experimental paradigm

It might be argued that our paradigm not only manipulated WM load, but also the division of attention during trials; in the high WM load condition, more attention is devoted to the WM task and less to LTM encoding, and therefore LTM is worse in the high WM load condition. Indeed, previous studies have shown that divided attention impairs LTM encoding (Kensinger *et al.*, 2003; Uncapher & Rugg, 2005) and that a high WM load interferes with selective attention (De Fockert *et al.*, 2001). Although subjects were required to indicate the sex of the face stimulus during encoding, which guaranteed at least some level of attention to this item, we cannot rule out that attention differs between the high and the low WM load condition. However, the concepts of selective attention and WM are in principal closely related, and the underlying processes are probably similar (D’Esposito *et al.*, 1995; Fuster, 1995; LaBar *et al.*, 1999; De Fockert *et al.*, 2001; Postle *et al.*, 2004). Thus, the possible confound between attention and the WM load manipulation is not a flaw of our specific paradigm, but

stems from the fundamental proximity of the underlying concepts and processes.

It is possible that the differential number of items processed in the WM task did not only influence WM load, but was also associated with different encoding strategies. For example, a single item could have been maintained visually, whereas maintenance of three items may have been accomplished via a verbal code. These different strategies may also have influenced the difference in neural activity between these conditions. Additional studies with different types of stimuli and encoding instructions will be necessary to isolate the specific contribution of memory load on neural activity during encoding.

It might be suggested that the relatively poor performance in the LTM task is due to disease-related factors in these patients, i.e. that these patients had brain lesions and received anti-epileptic medication. Indeed, overall behavioural performance is likely to be compromised by these factors. However, it is unlikely that our ERP and time–frequency results are significantly affected because only patients with unilateral pathology were included. It has been shown at least for simple visual and auditory detection tasks that recordings from the contralateral hemisphere of these patients are qualitatively similar to recordings from healthy monkeys (Paller *et al.*, 1992). Furthermore, several studies have reported converging results in iEEG in epilepsy patients and blood oxygen-level-dependent (BOLD) responses in healthy control subjects (e.g. Mukamel *et al.*, 2005; Axmacher *et al.*, 2007).

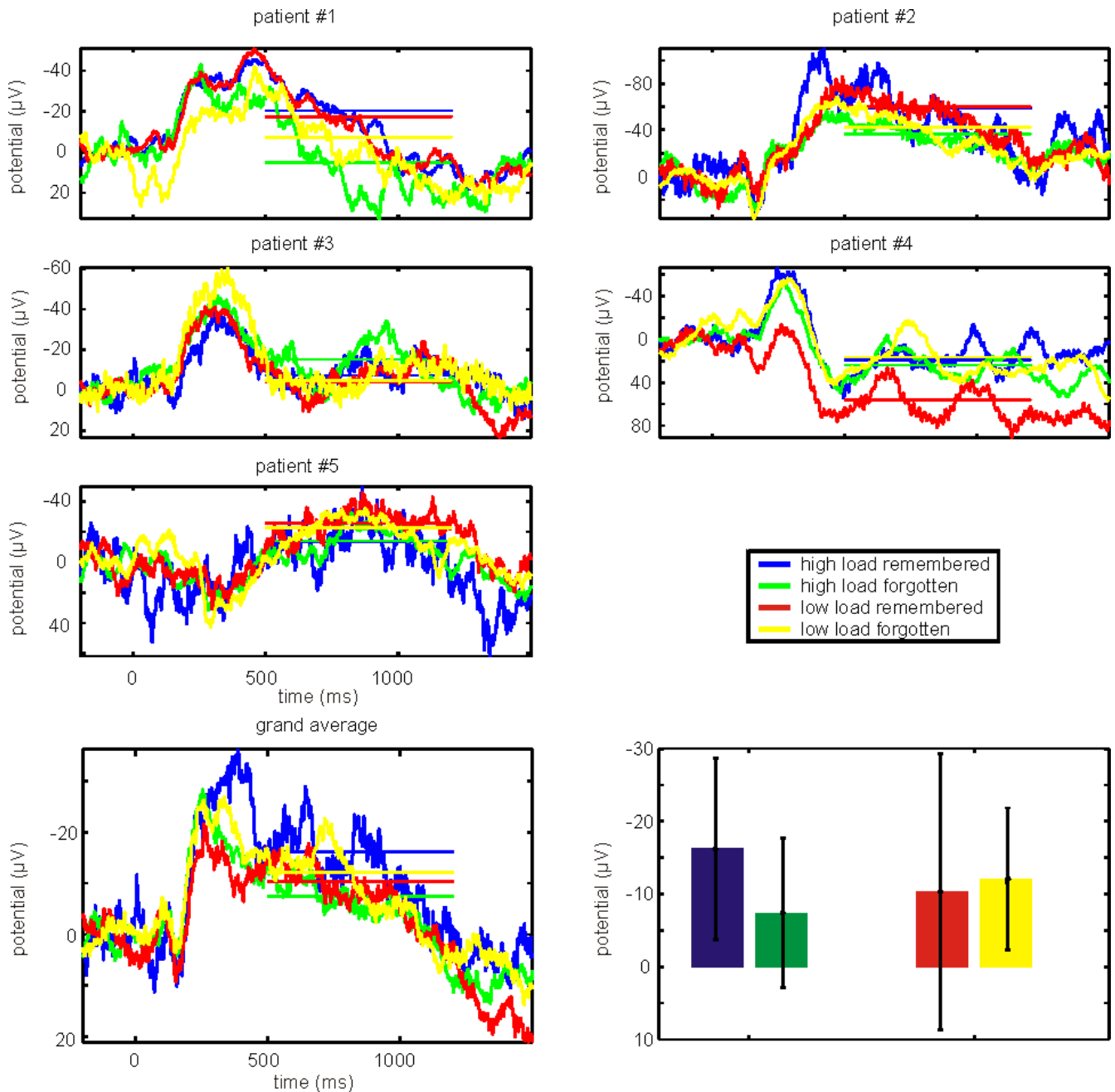


FIG. 5. ERPs in the rhinal cortex. ERPs averaged across all rhinal contacts are shown both for each subject and averaged across subjects (bottom). For the hippocampal ERPs, events are triggered to the onset of the face stimulus which had to be encoded into LTM. The lines indicate averaged slow potentials between 500 and 1200 ms. In contrast to the hippocampus, there was no load effect on rhinal potentials. Error bars depict SEM across subjects.

Slow event-related potentials

A number of previous iEEG studies investigated neural activity during LTM encoding and WM maintenance in the human hippocampus. Slow hippocampal ERPs differentiated between items which were subsequently recalled and subsequently forgotten starting after around 500 ms (Fernandez *et al.*, 1999). During maintenance of a single item in WM, positive slow potentials were observed, which turned increasingly negative when multiple items were being maintained (Axmacher *et al.*, 2007). In contrast to earlier ERPs such as the hippocampal P300 potential, which correspond to transient changes of neural activity (Makeig *et al.*, 2002; Fell *et al.*, 2004), these slow

potentials probably correspond to the sustained modification of firing rate in the MTL, as has been described in animals during WM maintenance (Suzuki *et al.*, 1997; Young *et al.*, 1997). It should be noted, though, that the relationship between activity within the hippocampus and the direction of slow potentials is probably quite complex. In hippocampal brain slices from the rat, slow potentials are related to accumulation of extracellular potassium under various pathological conditions (e.g. Zuckermann & Glaser, 1969; Aitken *et al.*, 1991). These increases in potassium concentration are due to an increase in persistent activity, in particular of glutamatergic (excitatory) cells (Speckmann & Elger, 1999). Recently, we observed slow potentials in the human hippocampus during a WM task (Axmacher

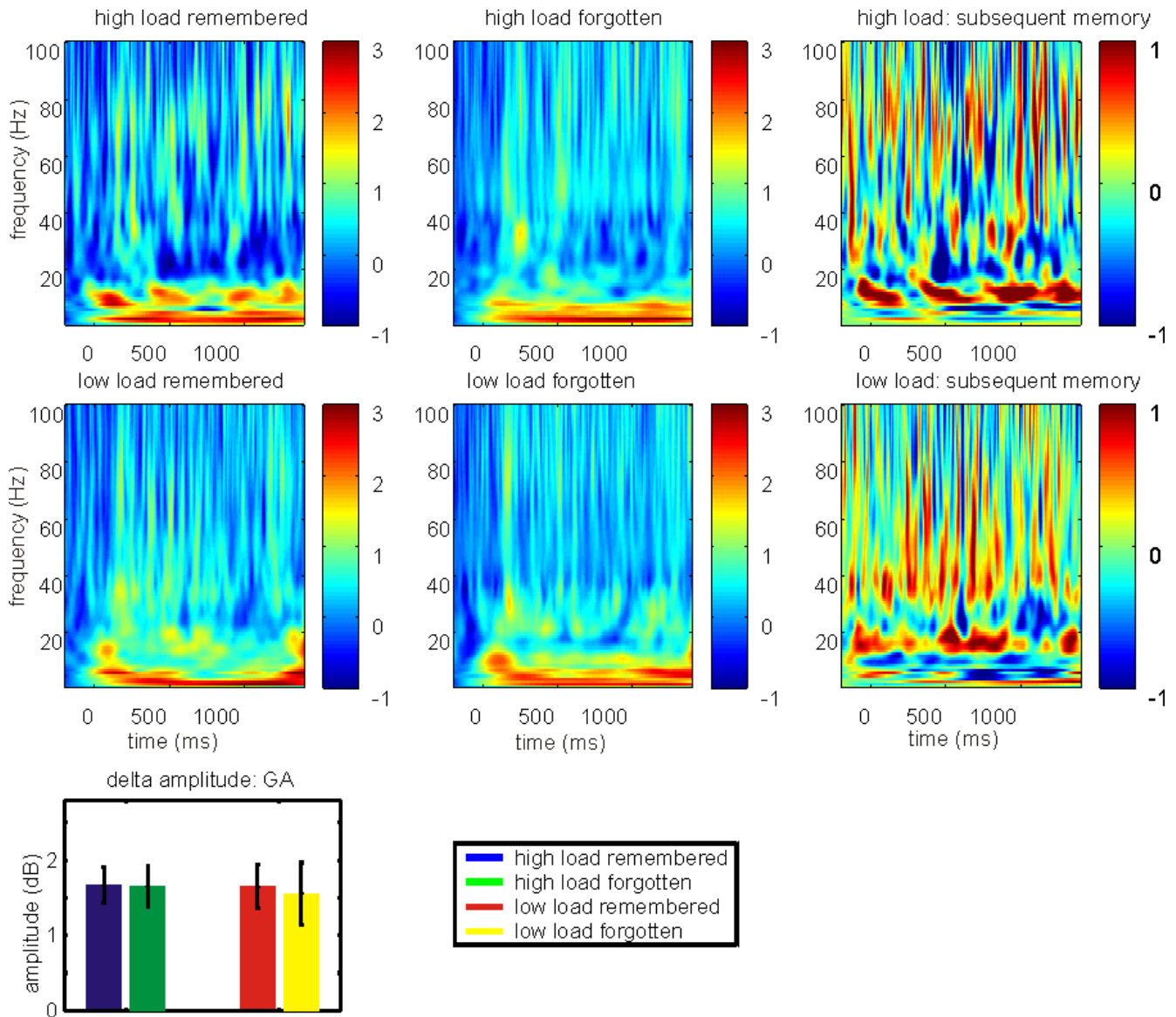


FIG. 6. No effect of WM load or subsequent LTM on oscillatory activity in the rhinal cortex. Amplitudes extracted by wavelet decompositions in the different conditions, as depicted for the hippocampus. Bottom: rhinal delta band activity did not change between conditions. Error bars depict SEM across subjects.

et al., 2007); to our knowledge, this was the first observation of slow hippocampal potentials during a cognitive task. In this situation, more negative slow potentials were associated with increased activity in the gamma frequency range, indicating that these potentials arise from synchronized activity patterns rather than just an increase in uncorrelated activity. Interestingly, gamma band activity (coupled with specific phases of theta oscillations) has been suggested to support WM maintenance of individual items in an influential modelling study (Lisman & Idiart, 1995; Jensen & Lisman, 2005), although this still awaits direct experimental confirmation. It is possible, however, that increasingly negative DC potentials and enhanced gamma band activity reflect the increased recruitment of cell assemblies synchronized in the gamma frequency range.

More ample evidence exists on the mechanisms underlying neocortical slow activity, which has been related to the allocation of cognitive resources to a particular task (for a review, see Rösler *et al.*, 1997). The biological mechanisms underlying these potentials and their relationship to the BOLD signal have been reviewed by Khader

et al. (2008). A novel mechanism underlying neocortical slow potentials was described by Mazaheri & Jensen (2008), who found in a magnetoencephalography study that slow potentials arose from asymmetric amplitude modulations of cortical oscillations. Neocortical slow potentials were also observed in category-specific regions during WM maintenance (Khader *et al.*, 2007). In that study, the same negative potentials were even more pronounced if items were subsequently remembered, suggesting similar processes during WM maintenance and LTM encoding (see below): persistent activation of neocortical stimulus representations may be triggered by attentional control systems and support WM maintenance (Cowan, 1999), but may also induce synaptic plasticity within the reactivated network, which would be beneficial for LTM encoding.

The relationship between hippocampal and neocortical slow potentials remains unclear. It is possible that persistent activation of the hippocampus as the most important structure for declarative memory formation is directly related to mnemonic processes, whereas slow neocortical potentials reflect a reactivation of content-specific

neocortical representations. This hypothesis would predict that memory-related hippocampal and neocortical slow potentials should be closely related, which could be tested in studies using simultaneous intracranial and scalp EEG recordings (e.g. Fell *et al.*, 2007). Such a direct comparison may also help our understanding of the different temporal characteristics of hippocampal and neocortical slow potentials (Rösler *et al.*, 1997; Khader *et al.*, 2008).

In the current study, we only observed an effect of WM load, but not of subsequent LTM, on slow hippocampal potentials. The apparent discrepancy to the results of Fernandez *et al.* (1999) might be explained by the different tests of LTM: whereas Fernandez and colleagues investigated free recall of words, recognition memory for faces was tested in our study. It has been shown that encoding leading to free recall activates the hippocampus to a stronger degree than encoding leading to recognition memory (Staresina & Davachi, 2006). This may also be reflected in the subsequent memory effects of slow potentials. Alternatively, the lack of a subsequent memory effect on ERPs in the current study might be related to the relatively poor memory performance, in particular in the high WM load condition. As described above, it was not possible to analyse 'sure old' and 'unsure old' responses separately because of the low number of trials. In the low load condition, ERPs during presentation of subsequently remembered items were on average more positive (Fig. 3). Although this difference did not reach significance, possibly because of the small group size, it would be consistent with previous data (Fernandez *et al.*, 1999).

Delta band activity

Several studies indicate a link between delta band activity and memory processes. It has, for instance, been observed that increased neocortical delta power is inter- and intra-individually correlated with reduced performance in verbal learning and continuous word recognition tasks (Foster *et al.*, 2008; Van Strien *et al.*, 2005). Klimesch *et al.* (2006) investigated the time course of oscillatory activity in a continuous word recognition paradigm. Apart from an early decrease of parietal theta band activity (between 4 and 6 Hz) after presentation of a correctly memorized word, they observed a late reduction of power in the delta band (with a maximum of 2.5 Hz) which was localized (using low-resolution brain electromagnetic tomography) to the MTL. These data are consistent with our finding of reduced delta band activity during successful memory encoding in the low load condition, because in both studies, decreased delta band activity was associated with increased recruitment of mnemonic processes.

However, regarding multi-item WM, a cortical enhancement of delta power was observed during a Sternberg task compared with a perceptual control condition by Harmony *et al.* (1996). Interestingly, the delta power increase was greater during the high WM load condition (maintenance of five digits) than during the low load condition (maintenance of three digits). This result is in accordance with our finding that delta band amplitude for later remembered items is greater during the high than during the low WM load condition. A similar link between delta activity and memory processes has been suggested on the conceptual level. Jensen & Lisman (2005) proposed that phase-amplitude coupling between slow (delta and theta) and fast (gamma) oscillations constitutes a mechanism underlying the representation of multiple items in WM and LTM. Indeed, it has been shown that the phase of delta oscillations modulates the power of theta and gamma oscillations, as well as neural firing rates (Lakatos *et al.*, 2005, 2008; Jacobs *et al.*, 2007). The strength of this

modulation depends on the amplitude of the low-frequency oscillation (e.g. Jacobs *et al.*, 2007). In this sense, high delta amplitude may be necessary for correct WM and LTM processing in the high load (i.e. multi-item) condition, because it increases the signal-to-noise ratio of delta phase information and enables reliable phase-amplitude coupling.

A number of intracranial EEG studies have investigated the effect of LTM formation and WM maintenance on oscillatory high-frequency activity. Hippocampal gamma band activity in the lower frequency range (32–48 Hz) was reduced during LTM formation (Fell *et al.*, 2001), while activity in higher frequency ranges was increased (44–64 Hz; Sederberg *et al.*, 2007). WM maintenance involved an increase of broad-band high-frequency activity between 20 and 100 Hz in the hippocampus (Axmacher *et al.*, 2007); a similar effect was also observed in two patients with subdural neocortical electrodes (Howard *et al.*, 2003). As already mentioned above, these results may be explained by an influential computational model, which suggests that individual items in WM are being represented by individual cycles of gamma band activity during consecutive phases of low-frequency oscillations (Lisman & Idiart, 1995; Jensen & Lisman, 2005).

A large number of studies have investigated differential activity during encoding of items as a function of later memory for those items. These studies suggest several consecutive processing steps during successful memory encoding: activity during early steps of encoding depends on specific stimulus properties such as its size or colour and is thus most likely related to the effective initial representation of the item. Later encoding steps recruit the medial temporal lobes, where multiple stimulus features are bound together and linked with previous experience (Paller & Wagner, 2002). The hippocampus, in particular, appears to be recruited whenever information from multiple sources needs to be integrated, irrespective of the exact stimulus properties involved. Several functional MRI (fMRI) studies reported increased BOLD responses during presentation of subsequently remembered as compared with forgotten items in the MTL (e.g. Brewer *et al.*, 1998; Wagner *et al.*, 1998). However, while BOLD responses appear to be positively correlated with oscillatory activity in higher (e.g. gamma) frequency ranges (e.g. Logothetis *et al.*, 2001; Mukamel *et al.*, 2005), a negative correlation with activity in the delta band was described (Czisch *et al.*, 2004; Mäkiranta *et al.*, 2004; Mukamel *et al.*, 2005), consistent with our finding of a reduced delta band activity for subsequently remembered items in the low load condition (Fig. 4).

Interaction of WM and LTM

Our paradigm was designed to investigate the impact of WM load on the simultaneous encoding of other items into LTM. It therefore differs from previous studies on the influence of WM maintenance on the encoding of the same item, which showed that activation of the MTL during WM was predictive for later memory of that item (Schon *et al.*, 2004; Ranganath *et al.*, 2005). These findings suggest that the same process is engaged in WM maintenance and LTM encoding; mechanistically, persistent activations of stimulus-specific neurons might support the formation of memory traces by long-term plasticity of synaptic connections. On the other hand, reverberant activity in neural networks during WM may also be detrimental for the neural basis of LTM encoding, because synaptic plasticity depends on the exact timing of action potentials (e.g. Dan & Poo, 2004). Indeed, we recently found in a fMRI study that activation of the MTL during a WM task involving a complex manipulation was only predictive for LTM recognition if the WM task was successfully completed, which

depended on correlated activity between the MTL and adjacent temporal regions (Axmacher *et al.*, 2008a). The current study further helps to elucidate the interactions between WM and LTM: not only do unsuccessful attempts to execute a WM task interfere with LTM encoding, but so too does maintenance of multiple other items.

The effect of WM maintenance on LTM encoding might be caused by deeper encoding if the same items were maintained in WM or shallower encoding if other items were maintained, as suggested by the level of processing theory (Craik & Lockhart, 1972). It has been demonstrated that processes within the prefrontal cortex are crucial for WM maintenance; for example, in a verbal WM task, connectivity between prefrontal cortex and content-specific regions in inferior temporal cortex was enhanced by memory load (Fiebach *et al.*, 2006). However, the MTL also appears to be relevant for attentional processing of stimuli in WM, because several previous studies have demonstrated that medial temporal activity during WM maintenance predicts subsequent memory for these items (Schon *et al.*, 2004; Ranganath *et al.*, 2005; Axmacher *et al.*, 2008a). In the current study, only hippocampal and rhinal potentials could be investigated because patients were only implanted in these regions. In contrast to the results from the hippocampus, we did not observe a load effect in the rhinal cortex (Fig. 5). It has been proposed that recognition memory relies on two separable processes, recollection and familiarity, and that these processes have dissociable neural correlates in the medial temporal lobe (e.g. Brown & Aggleton, 2001; Ranganath *et al.*, 2004; Montaldi *et al.*, 2006; Diana *et al.*, 2007). These studies suggest that recollection relies on activity within the hippocampus, while anterior parahippocampal regions such as the rhinal cortex support familiarity. Following this line of reasoning, the absence of a load effect on ERPs and time-frequency activity in the rhinal cortex may indicate that LTM recognition in our study is mainly due to successful recollection and not familiarity. On the other hand, memory performance was in general relatively low, and most responses were given with low confidence, which suggests that they actually rely on familiarity rather than recollection. In fact, several studies question a double dissociation between familiarity and recollection altogether and instead support the idea that recognition involves a single, hippocampus-dependent process with different degrees of confidence (e.g. Squire *et al.*, 2007; Shrager *et al.*, 2008). Moreover, single-unit recording studies in human epilepsy patients show that the firing rate of individual hippocampal cells during recognition contains information on both item familiarity and conscious recollection of this item (Rutishauser *et al.*, 2008). Given these complexities and the fact that we did not directly distinguish between familiarity and recollection, our data do not lend support to either the single process or the dual-process view on recognition memory.

It is well established that the hippocampus is necessary for LTM encoding, and several lines of evidence suggest that it is also relevant for WM. However, this of course does not exclude that other regions (e.g. the prefrontal cortex; Blumenfeld & Ranganath, 2006) also play an important role, or even that the observed hippocampal activity is functionally irrelevant. Furthermore, it is possible that the observed difference in hippocampal delta activity for subsequently remembered and forgotten items supports memory encoding not directly via mnemonic processes, but is beneficial for other reasons.

We related maintenance of multiple items to the maintenance of associations because in both cases, more information needs to be temporarily stored in WM as compared with the situation of a single item. In functional imaging experiments, the hippocampus shows increased activation both during maintenance of multiple items as compared with a single item (Axmacher *et al.*, 2007), and during maintenance of associations between item features as compared with a

single item (Piekema *et al.*, 2006). These activations appear to be functionally relevant, because patients with hippocampal lesions are impaired in WM tasks involving associations of multiple item features (Hannula *et al.*, 2006; Olson *et al.*, 2006), but not in tasks requiring maintenance of individual items (Cave & Squire, 1992).

LTM encoding of an item which is simultaneously being maintained in WM may be differentially affected if other items are being maintained at the same time and if the item is associated with other items: whereas maintenance of multiple items may distract from encoding of each individual item, maintenance of associations between items may be beneficial for LTM encoding of the associated items. However, the latter effect may also depend on the specific LTM paradigm – associative processing is particularly beneficial if these associations are afterwards tested, but not necessarily for subsequent recognition of individual items (e.g. Blumenfeld & Ranganath, 2006). Moreover, association of two items will most likely also impair LTM encoding of an unrelated third item. In our paradigm, we did not test LTM of items which were maintained in WM, but of other unrelated items which were presented during the delay phase.

Conclusions

Speculatively, we suggest the following scenario, which is based on a previous review (Axmacher *et al.*, 2008b). LTM encoding is associated with positive late ERPs in the hippocampus (Fernandez *et al.*, 1999) and more positive neocortical ERPs (e.g. Fernandez *et al.*, 1998). These slow positive shifts are probably linked to reductions of hippocampal and neocortical activity, respectively (Birbaumer *et al.*, 1990; Rösler *et al.*, 1997; Speckmann & Elger, 1999). In monkeys, hippocampal (Wirth *et al.*, 2003; Yanike *et al.*, 2004) and neocortical (Li *et al.*, 1993; Rainer & Miller, 2000; Baker *et al.*, 2002; Freedman *et al.*, 2006) stimulus representations become sparser during learning, which lends additional support to the hypothesis that memory formation is linked to inhibition. As the integrity of the hippocampus is necessary for these tasks, we suggest that inhibition of hippocampal and neocortical activity actually plays a functional role for LTM encoding. This latter assumption is still speculative, because a causal role of these processes has not been proven. We have shown in this and a previous study (Axmacher *et al.*, 2007) that WM load induces negative shifts of long-lasting ERPs in the hippocampus. As described above, this effect is probably due to sustained increases of neural activity. Thus, LTM formation and multi-item WM maintenance are associated with hippocampal neural correlates of opposite directions. This suggests that WM-related negative shifts may interfere with simultaneous encoding of other events and may thus be related to the impaired LTM encoding in this condition; we cannot exclude, however, that other regions contribute to this effect as well. The interference between LTM and WM load is reflected by the amplitude of delta oscillations. Under a low WM load, correct LTM performance seems to be related to a reduction of delta activity, which is in accordance with prior studies indicating improved memory processing with diminished delta power (Van Strien *et al.*, 2005; Klimesch *et al.*, 2006; Foster *et al.*, 2008). Under a high WM load, however, the role of delta band activity is different, as indicated by the 'load' × 'memory' interaction in this frequency range and the absence of a subsequent memory effect in the high WM load condition.

Similar controversial roles of neural activity within a certain brain region for LTM formation have been observed in fMRI studies: activation in the dorsolateral prefrontal cortex is usually associated with subsequent forgetting of items (Wagner *et al.*, 1998; Otten & Rugg, 2001), but may become beneficial for LTM encoding if inter-

item associations are being encoded (Blumenfeld & Ranganath, 2006). The BOLD response in the medial temporal lobe is enhanced for subsequently remembered items which are rehearsed in WM during LTM encoding (Schon *et al.*, 2004; Ranganath *et al.*, 2005; Axmacher *et al.*, 2008a), but activity in the same region is detrimental for LTM encoding if WM fails (Axmacher *et al.*, 2008a). Taken together, these findings indicate that activity within a given region, such as hippocampal delta band activity, may either facilitate or disturb LTM depending on the encoding situation.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Averaged hippocampal activity for a subset of patients.

Fig. S2. Time–frequency plots for oscillatory activity during LTM encoding in the high and the low WM load condition in each individual subject.

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Abbreviations

BOLD, blood oxygen-level-dependent; DC, direct current; ERPs, event-related potentials; fMRI, functional magnetic resonance imaging; iEEG, intracranial electroencephalography; LTM, long-term memory; MTL, medial temporal lobe; WM, working memory.

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