

Interaction of Working Memory and Long-Term Memory in the Medial Temporal Lobe

Nikolai Axmacher^{1,2}, Daniel P. Schmitz^{1,3}, Ilona Weinreich³,
Christian E. Elger^{1,2} and Juergen Fell¹

¹Department of Epileptology, University of Bonn, 53105 Bonn, Germany, ²Life and Brain Center of Academic Research, 53127 Bonn, Germany and ³Department of Applied Mathematics, University of Applied Sciences, Remagen, D-53424 Germany

Recent findings indicate that regions in the medial temporal lobe (MTL) do not only play a crucial role in long-term memory (LTM) encoding, but contribute to working memory (WM) as well. However, very few studies investigated the interaction between these processes so far. In a new functional magnetic resonance imaging paradigm comprising both a complex WM task and an LTM recognition task, we found not only that some items were successfully processed in WM but later forgotten, but also that a significant number of items which were not successfully processed in the WM task were subsequently recognized. Activation in the parahippocampal cortex (PHC) during successful WM was predictive of subsequent LTM, but was correlated with subsequent forgetting if the WM task was not successfully solved. The contribution of the PHC to LTM encoding thus crucially depends on whether an item was successfully processed in the WM task. Functional connectivity analysis revealed that across-trial fluctuations in PHC activity were correlated with activation in extensive regions if WM and LTM tasks were correctly solved, whereas connectivity broke down during unsuccessful attempts to do the task, suggesting that activity in the PHC during WM has to be well controlled to support LTM formation.

Keywords: fMRI, long-term memory, medial temporal lobe, working memory

Introduction

Traditionally, the formation of declarative long-term memory (LTM) and the short-term maintenance of items in working memory (WM) have been attributed to distinct memory systems and localized in different brain regions (Atkinson and Shiffrin 1968; Squire 1992). Recently, however, this seemingly clear distinction between LTM processes in the medial temporal lobe (MTL) and WM processes in other regions was questioned (Ranganath and Blumenfeld 2005). A variety of articles reported a contribution of the MTL to implicit memory (Degonda et al. 2005) as well as WM processes (Ranganath and D'Esposito 2001; Stern et al. 2001). Prior recordings in the parahippocampal cortex (PHC) of animals have indeed revealed evidence for sustained modifications of firing rates that outlast stimulus presentation (Suzuki et al. 1997; Young et al. 1997). These effects are reminiscent of a neural correlate of short-term maintenance. Furthermore, sustained cellular activity is a major inductor of long-term potentiation, the suggested possible cellular substrate of LTM formation (Bliss and Lomo 1973). Finally, active maintenance of stimulus representations is crucial for LTM formation in computer models of the MTL (Jensen and Lisman 1996; Hasselmo et al. 2002).

Following these reports of a contribution of the MTL to WM maintenance, the validity of a double-dissociation between WM and LTM processes has been questioned (Ranganath and Blumenfeld 2005). Indeed, it is possible that processes in the MTL not only contribute to some WM tasks, but are even necessary for them. This is suggested by recent clinical studies on patients with lesions in the MTL, which revealed impairments in WM tasks (Hannula et al. 2006; Nichols et al. 2006; Olson et al. 2006). Although these findings support the concept of a shared neural substrate of WM and LTM, it is still an open question whether the same neural mechanism underlies both processes. More specifically, it is possible that the persistent neural activity during WM maintenance is a necessary prerequisite for LTM formation; alternatively, LTM formation might occur via different pathways, only 1 of which involves successful WM maintenance. Although it has been shown that activation of the PHC during correctly performed WM is indeed predictive of later item recollection (Schon et al. 2004; Ranganath, Cohen, et al. 2005), it is not clear whether the PHC similarly supports LTM formation for items which are not successfully processed in WM (throughout the text, the phrases “successfully processed” or “successfully solved” WM trials correspond to correct trials). Previous studies on the interaction of WM and LTM most often used relatively simple WM paradigms in which subjects reached ceiling performance (e.g., Schon et al. 2004; Blumenfeld and Ranganath 2006). A comparison of LTM with and without successful WM requires, however, that WM fails in a significant fraction of trials. We thus designed a functional magnetic resonance imaging (fMRI) paradigm comprising a demanding WM task in which subjects should both maintain semantic information of words and count the number of letters. To further enhance WM load, the task was conducted while an independent list of words was maintained. This design allowed to compare activity during LTM formation of items which were successfully processed in the WM task with items where WM failed.

Materials and Methods

Subjects

Thirty healthy subjects (19 women; mean age \pm SD: 30.0 \pm 10.4 years) participated in the study. They were recruited from the University of Bonn as well as via newspaper. The study was approved by the local medical ethics committee, and all subjects gave written informed consent.

Experimental Paradigm

An overview of the experimental design is depicted in Figure 1. We aimed at constructing a demanding WM task, where a significant number of items was not successfully processed. An extended description of designs which were conducted during the piloting

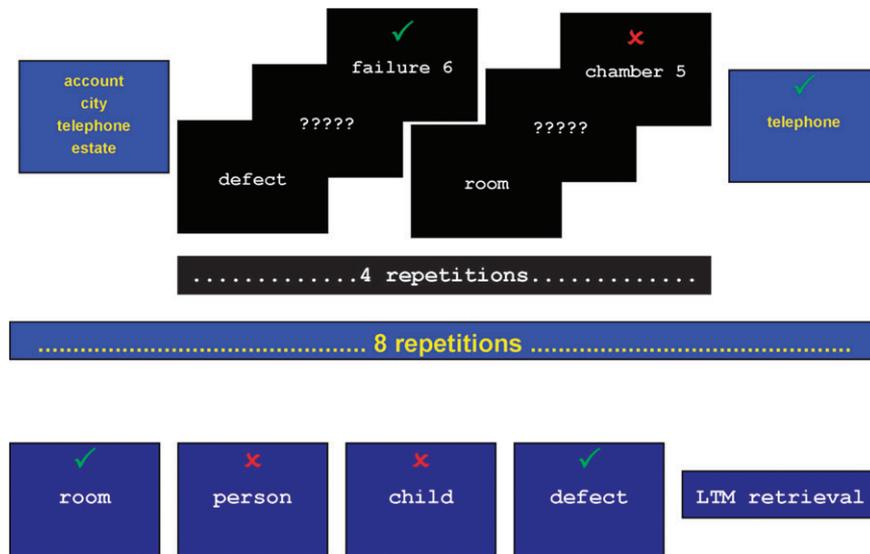


Figure 1. Overview of the paradigm. In the WM task, subjects had to count the number of letters in a word and to maintain the meaning of this word (white words on black screen). This task was aggravated as it was conducted during the maintenance phase of a Sternberg task involving a list of 4 words. In addition, LTM of the items in the modified delayed-match-to-sample (DMS) task was tested.

phase of our study and finally rejected is given in the Discussion. Briefly, the design comprised a combination of 3 tasks: 1st, a complex modification of a DMS task; 2nd, a Sternberg task with a list of words; 3rd, an LTM recognition task. We will 1st give an overview of the tasks and then turn to more specific details. In the DMS task, subjects had to process words simultaneously in 2 different ways: 1st, they had to count the number of letters; 2nd, they had to maintain the semantic content of the word. The probe in the DMS task consisted in another word and a number. Subjects pressed a button in their right hand if both of 2 conditions were fulfilled: the 2nd word was a synonym of the 1st word, and the number matched the number of letters in the 1st word. If only 1, or none, of these 2 conditions applied, subjects pressed a button in their left hand. The DMS task was performed during the maintenance phase of a surrounding Sternberg task. In the Sternberg task, subjects were presented a list of 4 words which they had to maintain. After 4 trials of the internal DMS task, subjects saw a test word and had to indicate by button press whether it was 1 of the 4 items from the list of items in the Sternberg task. After this block has been run 8 times (comprising a total of 32 trials of the embedded DMS task), subjects were presented a list of words in an LTM recognition task. Subjects had to indicate whether they had seen these items previously as item in the DMS task by pressing the button in the right hand; otherwise, they pressed the button in the left hand. No words which had served as probes in the DMS trials and no words from the Sternberg task were used as distracters. For clarity, words were presented in a different font and on a differently colored background in each task.

Stimuli consisted of German words with a length of 4-9 characters and a word frequency above 50 per million, selected from a comprehensive database of German words (CELEX). Words with matching semantics (i.e., synonyms) were selected from an internet-based database. Stimuli were presented via MRI-compatible goggles (Nordic Neuro Lab, Norway) using E-Prime software (Psychology software tools, Pittsburgh, PA). The list of words in the surrounding Sternberg task was presented for 3000 ms. After a pause of 1000 ms, during which a cross was shown, the item in the 1st internal DMS task was presented for 500 ms, followed by a delay of variable length between 6000 and 8000 ms and the DMS probe (500 ms). Four DMS tasks were repeated before a 2nd pause of 1000 ms and finally the probe of the surrounding Sternberg task (2000 ms) followed. After 8 blocks of the Sternberg task, all items from the DMS task and an equal number of new items were presented for 2000 ms, and subjects indicated whether they had seen these items before. This list was followed by a break of 60 s, before the next list of Sternberg items was shown. Thus, a total of 192 items was tested for

both WM and LTM (in 6 blocks of 32 words). We used multiple blocks instead of a single surprise recognition session at the end of the entire experiment to increase LTM performance.

Recordings and Analyses

Sixteen axial slices were collected at 1.5 T (Avanto, Siemens, Erlangen, Germany). We collected 1370 T_2^* -weighted, gradient echo EPI-scans, including 5 initial scans that were discarded to achieve steady-state magnetization (slice thickness: 3 mm; interslice gap: 0.3 mm; matrix size: 64 × 64; field of view: 192 mm; echo time: 40 ms; repetition time: 2650 ms).

MRIs were processed using SPM2 (www.fil.ion.ucl.ac.uk/spm/), and the following steps were performed: 1) Realignment with 3-dimensional motion correction and unwarping of interactions between motion artifacts and the magnetic field. 2) Normalization onto the MNI-atlas (Montreal Neurological Institute). 3) Spatial smoothing with an 8-mm Gaussian kernel (full width at half maximum). 4) Modeling of the expected hemodynamic responses (box-car regressor in a general linear model, GLM) and convolution of the regressors with a canonical hemodynamic response function to represent brain physiology. We used regressors of 6 s length starting at the beginning of each DMS task, thus covering the initial stimulus presentation and a large proportion of the delay period; we did not attempt to separately model the presentation of the initial and test stimulus, because these were presented only for 500 ms. Even more importantly, stimulus maintenance presumably starts already at the moment the stimulus is being presented. In this design, there was a baseline period of 2- to 4-s length (depending on the randomized length of the delay period, which was 6-8 s) between the offset of the regressor of 1 DMS task and the onset of the subsequent regressor. We have chosen this approach as we expected sustained neural activity patterns during stimulus maintenance (Young et al. 1997; Axmacher et al. 2007). This design involves some overlap between the convolved regressors and hemodynamic response functions. However, collinearity between the DMS regressors (measured by the cosine of pairs of regressors) is in fact quite low and does not exceed average absolute values of 0.1 (with 0 indicating that regressors are orthogonal and 1 indicating that they are perfectly correlated). We even observed a slight negative linear dependence between the DMS regressors which probably results from the fact that pairs of DMS regressors are not always adjacent to each other but may be separated by 1 or 2 trials. This means that the average angles between DMS regressors are smaller than 96°, that is, pairs of DMS regressors are almost orthogonal ($\approx 90^\circ$); see Supplementary Figure 1. A 2nd independent GLM was run in which DMS trials during correctly

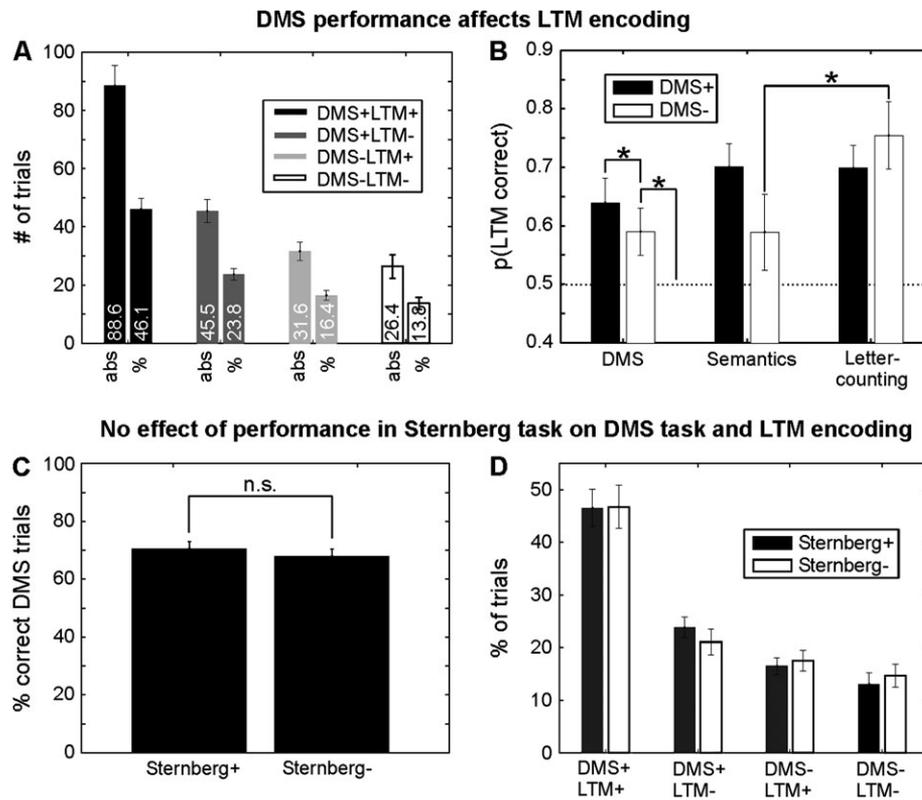


Figure 2. Behavioral results. (A) Absolute (“abs”) and relative (“%”) number of trials in each of the 4 conditions (DMS correct or incorrect, LTM correct or incorrect). (B) Probability of correct LTM recognition as a function of DMS performance, and as a function of correct performances in the semantic or letter-counting subpart of the DMS task. (C) Performance in Sternberg task did not affect performance of the DMS task. (D) Performance in Sternberg task did not affect the interaction between DMS performance and LTM performance.

and incorrectly solved Sternberg trials were modeled with separate regressors. 5) Temporal filtering of the acquired time series to reduce high- and low- frequency noise attributable to scanner drifts and physiological noise. 6) Calculation of parameter estimates for each condition covariate from the least mean squares fit of the model to the data. 7) Random-effects group analyses with subject as the random factor were performed with SPM2 on each regressor by entering the t -contrast images of each subject corresponding to a particular regressor into a 2nd-level 1-sample t -test. 8) Definition of contrasts. We investigated subsequent memory effects separately for DMS⁺ and DMS⁻ items by using the following contrasts: 1) subsequent memory for DMS⁺ items: DMS⁺LTM⁺ > DMS⁺LTM⁻; 2) subsequent memory for DMS⁻ items: DMS⁻LTM⁺ > DMS⁻LTM⁻; 3) subsequent forgetting for DMS⁺ items: DMS⁺LTM⁻ > DMS⁺LTM⁺; 4) subsequent forgetting for DMS⁻ items: DMS⁻LTM⁻ > DMS⁻LTM⁺. All figures with fMRI results are displayed using neurological convention (left hemisphere on the left side of the figure). To identify significant activations, we used an uncorrected threshold of $P < 0.001$ and a minimum cluster size of 5 contiguous voxels.

We have chosen this approach, which has been used in a large number of previous studies, as we had strong a priori assumptions that subsequent memory for DMS⁺ (WM⁺) items should activate regions in the MTL (Schon et al. 2004; Ranganath, Cohen, et al. 2005). Indeed, 1 main motivation of our study were recent findings that this brain region is not only crucial for LTM encoding, but appears to support some forms of WM maintenance as well, so that we hypothesized it to be the site of interaction between LTM and WM processes. Based on these assumptions, it can be regarded as overly conservative to correct for multiple comparisons in the entire brain. Time courses for each subject were extracted for the regions showing significant activations in the 2nd-level analysis using the Marsbar extension of SPM (Brett et al. 2002) and event-locked peristimulus time histograms were constructed.

Correlations between across-trial fluctuations of parameter estimates were calculated as described previously (Rissman et al. 2004). We investigated significant functional connectivity based on a functional ROI in the right PHC resulting from the contrast DMS⁺LTM⁺ > DMS⁻LTM⁻. Correlations were compared with a mathematically defined baseline of zero correlation instead of correlation during the pause periods, as even the resting brain shows significant connectivity during its “default mode” (Greicius et al. 2003). As in the univariate analysis, we used an uncorrected threshold of $P < 0.001$ and a minimum cluster size of 5 contiguous voxels.

Results

Behavioral Data

Our paradigm was designed to compare LTM encoding with and without successful WM processing. We 1st calculated the number of items that were successfully executed in the WM and the LTM task (Fig. 2). Only 46.1% of items were both successfully processed in WM and encoded into LTM (“DMS⁺LTM⁺”), and each of the other categories contained on average >26 items. We next calculated whether successful WM predicts LTM encoding, that is, whether the proportion of items which were correctly retrieved in the LTM task was higher for items which were successfully processed in the WM task (DMS⁺ items) than for those items where subjects gave an incorrect response in the WM task (DMS⁻ items). This prediction was confirmed ($t_{29} = 2.72$; $P < 0.01$; 1-tailed t -test). Next, we investigated whether LTM for items which were not successfully processed in the WM task failed because

subjects were not visually aware of these items, or whether these items were perceived but WM processing failed for some other reason. We found that the probability of LTM recognition for DMS⁻ items (59.0 ± 0.04%) was significantly better than chance (50%; $t_{29} = 2.40$; $P < 0.05$; 1-tailed t -test), which contradicts the interpretation that these items were not perceived at all. Finally, we calculated whether successful LTM encoding depends differently on successful execution of the semantic or the letter-counting aspect of the WM paradigm. In some trials, these 2 tasks could be separated (e.g., if the probe was a synonym of the cue while the number of letters was incorrect, and the subjects falsely responded “both criteria fulfilled,” the subject was most probably successful in the semantic, but not in the letter-counting task). Although there was no difference between the probability of successful LTM formation given that either the semantic or the letter-counting aspect was correctly processed ($t_{25} = 0.40$; $P > 0.05$; 2-tailed t -test), failure in the semantic aspect was associated with a significantly worse performance in the LTM task than failure in letter counting ($t_{25} = 2.41$; $P < 0.05$; 2-tailed t -test).

Finally, we investigated whether performance in the Sternberg task had an effect on performance in the DMS task and on LTM encoding of items in the DMS task. We 1st calculated whether the proportion of correct DMS trials was different during maintenance of correctly and incorrectly solved Sternberg tasks. There was no significant difference between these 2 conditions as revealed by a 2-tailed t -test ($t_{30} = 1.58$; $P > 0.1$; Fig. 2C). To exclude that performance in the Sternberg task had a specific effect on LTM encoding of items in DMS⁺ or DMS⁻ trials or affected the DMS × LTM interaction, we further

calculated a 3-way ANOVA with “Sternberg accuracy,” “DMS accuracy,” and “subsequent memory” as repeated measures. Although this analysis confirmed the effect of WM performance on LTM encoding reported in the manuscript (visible as a highly significant interaction between “DMS accuracy” and “subsequent memory”; $F_{1,30} = 26.899$; $P < 0.0001$), there was no main effect of “Sternberg accuracy” and, most importantly, no interaction of “Sternberg accuracy” with any other factor (“Sternberg accuracy” × “DMS accuracy”: $F_{1,30} = 2.491$; $P > 0.1$; “Sternberg accuracy” × “subsequent memory”: $F_{1,30} = 0.782$; $P > 0.3$; “Sternberg accuracy” × “DMS accuracy” × “subsequent memory”: $F_{1,30} = 0.836$; $P > 0.3$). These results strongly suggest that DMS performance and LTM encoding are not specifically affected by the Sternberg task (i.e., whether the Sternberg task is successfully solved or not).

FMRI Data: Univariate Analysis

Subsequent memory for DMS⁺ and DMS⁻ items was analyzed separately as described in the Methods section. Subsequent memory for DMS⁺ items (DMS⁺LTM⁺ > DMS⁺LTM⁻) was correlated with increased activation of the PHC bilaterally, with a preponderance of the right hemisphere (Fig. 3A; Talairach coordinates 21/-33/-11). Among the other activated regions were the bilateral insulae, the left midbrain and the left uncus hippocampi (Table 1). Furthermore, we observed that activity in the right PHC was significantly increased for subsequently *forgotten* DMS⁻ items (DMS⁻LTM⁻ > DMS⁻LTM⁺; Fig. 3B; Talairach coordinates 15/-29/-4). This contrast also yielded increased activation of the left middle and superior temporal gyrus and the middle frontal gyrus. None of the other

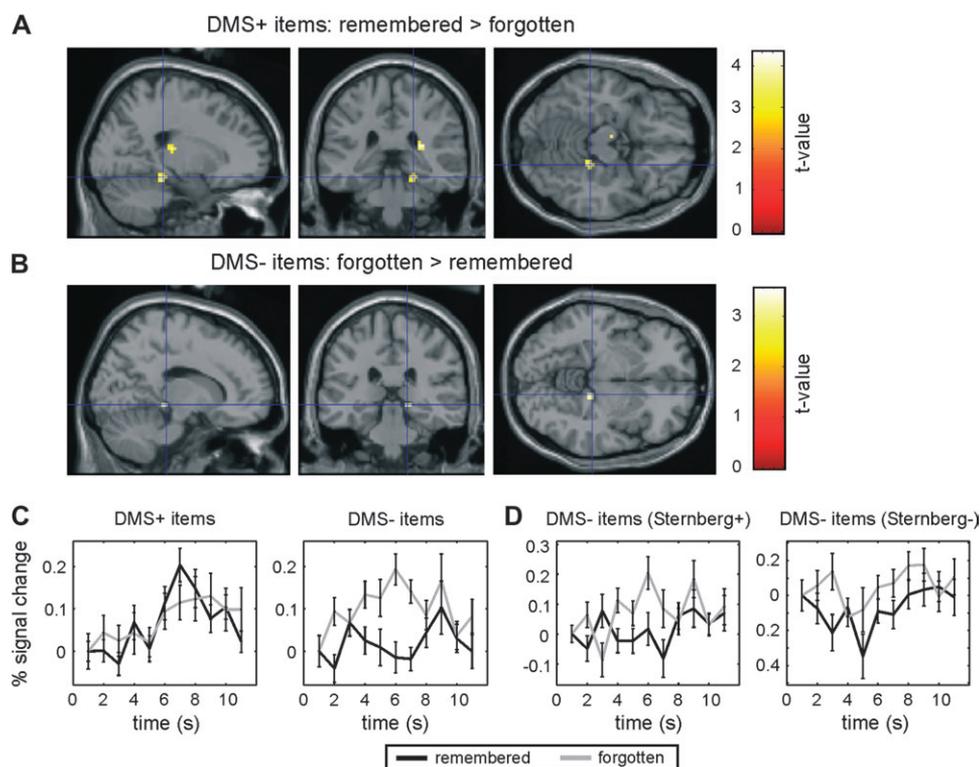


Figure 3. Subsequent memory and WM effects in the PHC. (A) Increased activation of the right PHC in the subsequent memory contrast of items with successful WM (DMS⁺ trials). (B) Activation of a similar cluster due to subsequent forgetting of items for which WM was not successful (DMS⁻ trials). (C) Peristimulus time histograms in the PHC cluster depicted in (A). (D) Time courses in the same region of interest for an alternative GLM, in which DMS trials during correctly and incorrectly solved Sternberg trials were modeled with separate regressors.

Table 1

Activated regions during WM and LTM tasks

Region	MNI coordinates				t-Value
	L/R	x	y	z	
DMS⁺LTM⁺ > DMS⁻LTM⁻					
Insula	R	30	-9	27	4.54
Midbrain	L	-6	-12	-18	4.45
Insula	R	27	-30	15	4.44
Uncus hippocampi	L	-33	0	-36	4.38
Parahippocampal gyrus	R	21	-33	-15	4.34
Inferior parietal lobule	L	-39	-45	27	4.12
Insula	L	-36	-15	21	3.99
Posterior cingulate cortex	R	30	-54	9	3.98
Caudate nucleus	R	15	15	12	3.89
Posterior cingulate cortex	L	-27	-48	27	3.81
Inferior frontal gyrus	R	36	21	-6	3.65
Inferior temporal gyrus	L	-42	-12	-33	3.53
Middle temporal gyrus	L	-48	-66	6	3.51
DMS⁻LTM⁺ > DMS⁻LTM⁻					
Postcentral gyrus	R	51	-30	39	4.14
Caudate nucleus	R	18	24	12	3.88
Inferior frontal gyrus	R	60	6	21	3.78
Thalamus	L	-9	-39	12	3.6
DMS⁺LTM⁻ > DMS⁻LTM⁺					
Cingulate gyrus	R	3	-15	36	4.19
Anterior cingulate cortex	L	-3	18	-3	3.92
Cingulate gyrus	L	-21	-36	45	3.57
DMS⁻LTM⁻ > DMS⁻LTM⁺					
Middle temporal gyrus	L	-60	-39	3	4.02
Middle frontal gyrus	R	30	12	39	3.91
Parahippocampal gyrus	R	15	-30	-6	3.62
Superior temporal gyrus	L	-36	18	-30	3.58

Note: The table provides an overview of significantly ($P < 0.001$ uncorrected) activated regions due to subsequent memory and subsequent forgetting effects for DMS⁺ and DMS⁻ trials.

contrasts induced a significant activation in medial temporal regions (DMS⁻LTM⁺ > DMS⁻LTM⁻: right postcentral gyrus, right caudate nucleus, right inferior frontal gyrus, left thalamus; DMS⁺LTM⁻ > DMS⁺LTM⁺: bilateral cingulate gyrus).

To test whether this “subsequent forgetting” effect for DMS⁻ items was present in the cluster defined by the subsequent memory effect for DMS⁺ items, we calculated the time course of activation in this cluster for both DMS⁺ and DMS⁻ items as a function of subsequent memory performance. Indeed, we found not only increased activity of subsequently remembered as opposed to forgotten DMS⁺ items, but also an even more prominent activity decrease during processing of subsequently remembered as opposed to forgotten DMS⁻ items (Fig. 3C, right column). It should be noted that these time courses were all derived from the cluster defined by the DMS⁺LTM⁺ > DMS⁺LTM⁻ contrast, indicating that both effects were apparent in the same region (even though the exact location of the cluster defined by this contrast and the cluster defined by the DMS⁻LTM⁻ > DMS⁻LTM⁺ contrasts were slightly different).

To address the question whether the subsequent forgetting effect in the PHC during DMS⁻ trials depends on performance in the Sternberg task, we ran an additional GLM where DMS trials during correctly and incorrectly solved Sternberg trials were separated (i.e., Sternberg⁺DMS⁺LTM⁺; Sternberg⁻DMS⁺LTM⁺, etc.). We extracted time courses for the same region of interest in the PHC as previously selected and found a subsequent forgetting effect for DMS⁻ items in this region, irrespective of the performance in the Sternberg task (i.e., for both Sternberg⁺ and Sternberg⁻ trials; see Fig. 3D).

fMRI Data: Functional Connectivity

These results indicate that activity in the PHC during a WM task has a different impact on LTM formation dependent on whether this WM task is successfully solved. To investigate this activation more closely, we calculated functional connectivity with the parahippocampal seed region by using the beta series correlation method of Rissman et al. (2004). The results are depicted in Figure 4. We found that activity within the seed region was significantly correlated with large regions in the temporal lobe in the DMS⁺LTM⁺ condition. Table 2 provides an overview of all significantly correlated regions. Most notably, we observed that activity within the seed region was significantly correlated with activity within the hippocampus only for trials with subsequently remembered words (i.e., in the DMS⁺LTM⁺ and the DMS⁻LTM⁺ conditions). The number of correlated voxels was reduced during the DMS⁺LTM⁻ and DMS⁻LTM⁺ condition, and was smallest during the DMS⁻LTM⁻ condition. To quantify the extension of correlated regions in the different condition, we calculated the number of voxels which showed significant correlation with the seed region in the right PHC (Fig. 5). For statistical purposes, we normalized the number of significantly correlated voxels over all conditions in each subject. Our analysis of functional connectivity mainly aimed at comparing the DMS⁺LTM⁺ and the DMS⁻LTM⁻ condition, which both induced a significantly higher PHC activation in the univariate analyses than the respective DMS⁺/DMS⁻ condition with the opposing LTM effect. We thus calculated a 2-tailed *t*-test of the number of voxels showing significant correlations with the seed region for these 2 conditions. We found that this number was significantly smaller in the DMS⁺LTM⁺ condition as compared with the DMS⁻LTM⁻ condition ($t_{30} = 5.78$; $P < 10^{-5}$). In addition, a 2-way ANOVA with “DMS” and “LTM” as repeated measures revealed main effects of both “DMS” ($F_{1,30} = 44.760$; $P < 0.0001$) and “LTM” ($F_{1,30} = 8.308$; $P < 0.01$). Furthermore, there was a significant “DMS” × “LTM” interaction ($F_{1,30} = 7.515$; $P < 0.05$), indicating a stronger impact of “LTM” on the number of correlated voxels for DMS⁺ as compared with DMS⁻ items.

It might be argued that the specific correlation between PHC and hippocampus for subsequently remembered trials and the change in the number of correlated voxels was due to the different number of trials between the conditions. We thus recalculated functional connectivity with an equal number of trials in each condition by randomly selecting trials from all conditions which contained more trials than the condition with the smallest number of trials (only subjects with at least 5 trials in each condition were taken into account, which resulted in 27 subjects). This resulted in qualitatively similar differences between the conditions (see Supplementary Fig. 2). Again, the number of correlated voxels was significantly smaller for DMS⁻LTM⁻ than for DMS⁺LTM⁺ trials ($t_{26} = 2.10$; $P < 0.05$; 2-tailed *t*-tests). A 2-way ANOVA revealed a significant effect of “DMS” ($F_{1,26} = 4.262$; $P < 0.05$), whereas the effect of “LTM” and the “DMS” × “LTM” interaction did not reach significance. In this analysis, correlation between the parahippocampal seed and the hippocampus reached significance in all conditions (Supplementary Table 1), arguing against the idea that correlation between these structures is the critical factor for successful LTM formation.

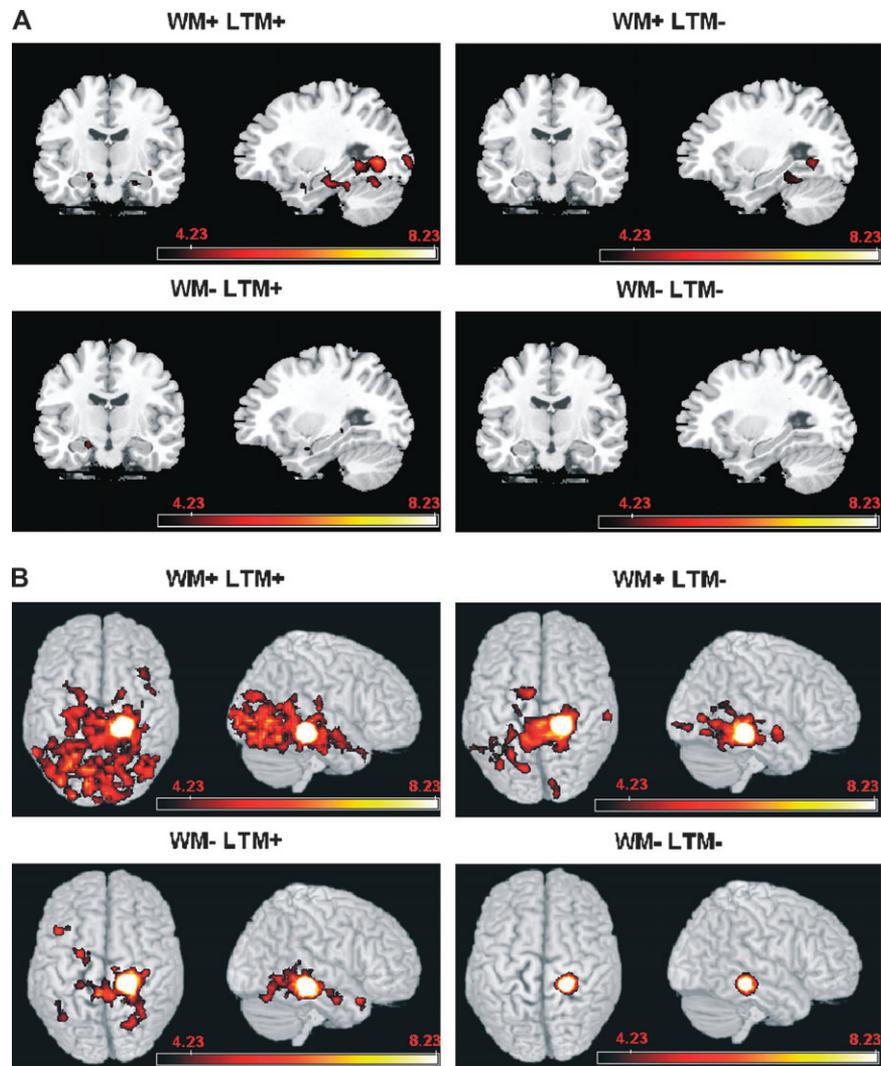


Figure 4. Functional connectivity with the PHC changes as a function of WM and LTM success. Although extended correlated regions were significantly correlated with intertrial BOLD fluctuations within the right PHC in the DMS⁺LTM⁺ condition, the size of these regions decreased when either the WM task or LTM recognition failed. (A) Projection of significantly correlated regions on coronal and sagittal brain slices. (B) Projection of the same regions on transparent brain.

Discussion

In our study, we aimed at comparing the processes underlying LTM formation for items which were successfully processed in a WM task with LTM formation for those items for which WM failed. This question required to build a design in which the WM task was not successfully solved for a considerable number of items. Performance usually drops with memory load in tasks which require the simultaneous maintenance of multiple items or when an n-back procedure is used. However, subsequent memory effects of individual items cannot be unambiguously traced in such designs. Alternatively, WM maintenance can be disrupted by the presentation of distracters during the maintenance phase (Sakai et al. 2002), but this makes the processes during the maintenance phase hard to interpret. We thus choose to employ a DMS task in which memory load was enhanced by a simultaneous semantic and letter-counting task. In a most parsimonious design, we combined a DMS task with a subsequent LTM recognition task. In the DMS task, subjects were required to count the number of letters in a word (between 4 and 9 characters) and to maintain the meaning of

the word, which had to be compared with a synonym to render this task more demanding; in addition, presentation times were rather short (200 ms). However, the percentage of incorrect trials in this design was still extremely low: only 2.7% of all DMS trials were both incorrectly solved during the WM task and not encoded into LTM, which amounts to an absolute number of 5.1 ± 1.2 DMS/LTM⁻ trials (mean \pm std. from 10 subjects); only 1 of 10 subjects had more than 10 DMS/LTM⁻ trials. This number is insufficient for an fMRI study. These results are in principle agreement with previous studies (for example, in the study by Schon et al. 2004, only <1% of the DMS trials received incorrect responses). Several possibilities to render this task more demanding were considered but finally rejected: 1st, presentation times could have been reduced. However, even with presentation times as low as 200 ms, the number of incorrect trials was not sufficient for an fMRI study, and even lower presentation times might have raised doubts whether the items had been consciously perceived at all. Second, we tried to make use of more complex items (fractals). In this case, however, LTM performance dropped significantly, so that we could not

Table 2

Results from the functional connectivity analysis

Region	MNI coordinates				t-Value
	L/R	x	y	z	
DMS⁺LTM⁺					
Lingual gyrus	L	-12	-87	-5	7.01
Middle occipital gyrus	L	-24	-99	-9	6.9
Cerebellum	L	-6	-74	-22	6.83
Brainstem	R	9	-30	-13	6.71
Inferior occipital gyrus	L	-36	-83	-19	6.71
Parahippocampal	L	-24	-30	-23	6.4
Lingual gyrus	R	9	-81	-1	6.34
Cerebellum	R	24	-73	-26	6.18
Hippocampus	R	24	-15	-15	6.17
Middle occipital gyrus	R	36	-72	6	6.13
Cerebellum		0	-43	-10	6.13
Posterior cingulate gyrus		0	-47	7	5.99
Middle occipital gyrus	R	49	-68	-11	5.96
Hippocampus	L	-21	-18	-19	5.93
Fusiform gyrus	R	30	-46	-13	5.83
Cuneus	L	3	-82	22	5.66
Thalamus	R	3	-22	12	5.65
Thalamus	L	-3	-28	-2	5.6
Middle occipital gyrus	R	49	-78	2	5.56
DMS⁺LTM⁻					
Cerebellum	R	9	-43	-10	7.32
Midbrain	R	3	-31	-2	6.81
Fusiform gyrus	L	-12	-46	-13	6.36
Basal ganglia	L	-9	-3	-11	6.07
Insula	R	52	-28	18	5.65
Cerebellum	R	21	-85	-30	5.55
DMS⁻LTM⁺					
Cerebellum	L	-6	-43	-20	6.97
Hippocampus	R	24	-21	-19	6.91
Parahippocampal	R	24	-46	-13	6.64
Cerebellum	R	6	-43	-10	6.28
Superior temporal	L	-42	17	-28	5.95
Midbrain	R	9	-18	-15	5.83
Fusiform gyrus	R	33	-58	-11	5.74
Midbrain	R	12	-14	-37	5.68
Amygdala	L	-24	-2	-29	5.52
DMS⁻LTM⁻					
Cerebellum	R	6	-42	-28	5.48

Note: Overview of significantly correlated regions in the different conditions. The seed region was chosen in the right PHC.

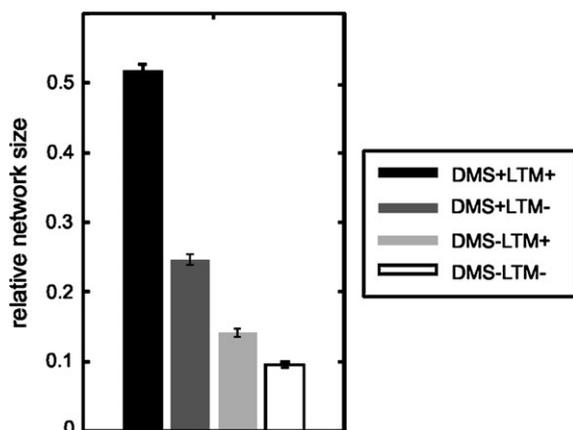


Figure 5. Decrease of the extension of correlated regions with failure in the WM or LTM task. Main effect of WM and LTM on the number of voxels which were significantly correlated with a seed in the PHC resulting from the contrast $DMS^+LTM^+ > DMS^+LTM^-$.

be certain about the successful encoding of these items. Third, longer delays could have been used. This might have been effective, but would have further increased the duration of the experiment, which was already rather long (~60 min; see

Methods). We thus choose to conduct the DMS task during the maintenance phase of a surrounding Sternberg task (see Fig. 1); possible pitfalls of this design are discussed below.

Behaviorally, a significantly larger proportion of items in correctly solved DMS trials than in incorrect DMS trials was encoded into LTM, as expected by previous findings that WM maintenance facilitates LTM encoding (Schon et al. 2004; Ranganath, Cohen, et al. 2005). This effect may be explained by an increased rehearsal of items in correct DMS trials; in incorrect trials, rehearsal probably broke down during the maintenance phase. On the other hand, there was no specific effect of performance in the surrounding Sternberg task on DMS performance and LTM encoding. This might be explained by assuming that both the successful and the unsuccessful attempts to perform the Sternberg task consume a similar amount of WM resources.

Some of the items from the Sternberg task may not only be maintained in WM until retrieval, but may also be encoded into LTM, which might affect DMS performance and/or LTM encoding of DMS items. LTM for the items in the Sternberg task was not tested in our paradigm, so that we cannot directly investigate this idea. However, we argue that it is unlikely that LTM encoding of Sternberg items significantly influenced DMS performance and/or LTM encoding of DMS items: LTM encoding of Sternberg items is probably strongly facilitated by WM maintenance of items in this task, similar to the finding in the DMS task and in previous studies (Schon et al. 2004; Ranganath, Cohen, et al. 2005). However, as reported above, there was no effect of performance in the Sternberg task on DMS performance and/or LTM encoding of DMS items. Actually, WM maintenance and LTM encoding are probably even more closely connected in the Sternberg task than in the DMS trials, because the maintenance phase was rather prolonged in the Sternberg task (37 s on average).

We found that activity in the PHC was predictive of subsequent LTM if it occurred during successful performance of a WM task, but correlated with worse LTM recognition if the WM task was not successfully solved. These data thus indicate that the contribution of this region to encoding of an item into LTM crucially depends on whether this item was successfully processed in the WM task. Functional connectivity analysis revealed that intertrial fluctuations in PHC activity were correlated with fluctuations in extensive regions if WM and LTM tasks were correctly solved, whereas connectivity broke down during unsuccessful attempts to do the task.

Although our design involved a twofold manipulation, it did not imply processing of inter-item relations. This might explain why we did not observe subsequent memory effects in the hippocampus proper at the given threshold. Although this result may appear surprising at 1st sight, it is consistent with the relational memory theory of the hippocampus which suggests a specific involvement of the hippocampus in memory tasks involving relational processes (Cohen and Eichenbaum 1993; Cohen et al. 1997; Henke et al. 1999; Eichenbaum 2000; O'Reilly and Rudy 2001). In contrast, we observed a subsequent memory effect in the PHC for DMS^+ items, similar to the findings of Davachi and Wagner (2002) who reported greater PHC, and decreased hippocampal, activity during item-based as compared with relational encoding. Parahippocampal, but not hippocampal, subsequent memory effects for items previously processed in a WM task have been described before (Schon et al. 2004; however, see Ranganath, Cohen, et al. 2005). In

addition, electrophysiological data from animal recordings indicated a greater role of the PHC than of the hippocampus in the preservation of information about individual items (Brown et al. 1987; Li et al. 1993). The location of the peak activation in our study was rather posterior as compared with the peak activation in some previous studies: in the study on the effect of WM maintenance on LTM encoding by Ranganath, Cohen, et al. (2005), their peak activation was in the hippocampus rather than in the posterior PHC. On the other hand, the study by Schon et al. (2004) also reports significant activation in regions which were similarly posterior as the activations observed in our study. We argue that 1 possible factor which might explain these differences is the different stimulus material: both studies mentioned above used trial-unique complex stimuli (3D-objects in the Ranganath et al. study; indoor and outdoor scenes in the Schon et al. study) which are more likely to activate anterior MTL regions like the hippocampus during WM than highly familiar stimuli like words, as used in our study (e.g., Stern et al. 2001).

Most importantly, we found that activity in the PHC correlated with *worse* LTM recognition if the WM task was not successfully solved. The peak activation for the $DMS^+LTM^+ > DMS^+LTM^-$ contrast and the $DMS^-LTM^- > DMS^-LTM^+$ contrast are nearby, but not identical (Fig. 3A,B). The time courses shown in Figure 3C are both derived from the $DMS^+LTM^+ > DMS^+LTM^-$ contrast. Indeed, the difference between the time courses corresponding to DMS^-LTM^- and DMS^-LTM^+ items is even more pronounced than the difference between the time courses of the DMS^+LTM^+ and DMS^+LTM^- items: in the region defined by the $DMS^+LTM^+ > DMS^+LTM^-$ contrast, the subsequent forgetting effect for DMS^- items is stronger than the subsequent memory effect for DMS^+ items (Fig. 3C). On the other hand, the number of adjacent voxels activated was larger in the $DMS^+LTM^+ > DMS^+LTM^-$ contrast than in the $DMS^-LTM^- > DMS^-LTM^+$ contrast (Fig. 3A vs. B). This apparent paradox is related to the fact that the DMS^-LTM^- and DMS^-LTM^+ time series in Figure 3C were computed in the region of interest defined by the $DMS^+LTM^+ > DMS^+LTM^-$ contrast: this region was slightly different from the region defined by the $DMS^-LTM^- > DMS^-LTM^+$ contrast (Fig. 3C). In the region in Figure 3A, not enough adjacent supra-threshold voxels reached the significance threshold for the $DMS^-LTM^- > DMS^-LTM^+$ contrast, but the average of all voxels in this region (even if not supra-threshold) resulted in a large time course difference for this contrast.

Interestingly, a subsequent forgetting effect in the PHC was observed by Davachi and Wagner (2002) for items which underwent relational encoding, which might suggest that the subjects in our task utilized relational encoding strategies during the unsuccessful attempts to solve the WM task. In our task, these strategies were not beneficial for the encoding of individual items, as indicated by the impaired recognition of DMS^- as compared with DMS^+ items. A similar dual (beneficial or detrimental) correlation of activation with subsequent memory has been observed in the dorsolateral prefrontal cortex (DLPFC); although activation of this region was correlated with subsequent forgetting in a variety of studies (e.g., Clark and Wagner 2003), it was correlated with *improved* LTM performance, and an increased BOLD response, if items were processed in an associative WM task (Blumenfeld and Ranganath 2006). Again, this divergent contribution of WM-related DLPFC activity to LTM formation has been interpreted as suggesting that DLPFC-related processing of interitem

relations might be beneficial or not to subsequent memory performance, depending on the memory task employed. More specifically, both Davachi and Wagner (2002) and Blumenfeld and Ranganath (2006) presented word triplets during encoding and investigated the recognition of information about all 3 words. Although a relational encoding strategy was indeed supportive of subsequent retrieval in this case, forming relations of the individual words in our paradigm probably does not promote encoding but rather distracts attention. Taken together, we suggest that PHC activation supports LTM formation of individual items if item characteristics have been extensively studied, as indicated by successful performance in our WM task, but that it can be detrimental for LTM formation if processing of these item-specific information fails.

It might be argued that even though there was no behavioral effect of performance in the Sternberg task on the DMS task, the LTM task, and the $DMS \times LTM$ interaction (Fig. 2C,D), our design with 2 interlaced tasks (the Sternberg and the DMS task) creates special strategy effects, proactive interference, or conflict-like behavior. Concerning proactive interference, it should be noted that each word was only used once (except, of course, for 2nd presentations during LTM recognition); most importantly, none of the words from the Sternberg task were used in the DMS task, so that at least itemspecific proactive interference due to previous presentation of an item can be excluded (e.g., Feredoes et al. 2006). However, it has been shown that WM span depends on performance in previous trials even if not exactly the same items are repeated (May et al. 1999). On the other hand, we actually intended to decrease the available capacity for WM processing in the DMS task by generating interference with the surrounding Sternberg task. To address the question whether the subsequent forgetting effect in the PHC during DMS^- trials depends on performance in the Sternberg task, we ran an additional GLM where DMS trials during correctly and incorrectly solved Sternberg trials were separated. The results depicted in Figure 3D show that the subsequent forgetting effect in the PHC occurs for both correctly ($Sternberg^+$) and incorrectly ($Sternberg^-$) solved Sternberg trials, strongly suggesting that proactive interference alone cannot explain this finding. Consistent with this result, we did not find any activation of the left inferior frontal gyrus (see Table 1), probably the most important area for proactive interference in WM (e.g., Feredoes et al. 2006; Jonides and Nee 2006). Of course, the interpretation of a negative finding in fMRI should not be overemphasized, as it might be due to insufficient statistical power.

Concerning effects of conflict processing more general, we argue that processing multiple items simultaneously in WM (or processing individual items while other items are being maintained, as in our study) always induces conflicting demands for resources: each item interferes with maintenance of each other item. Focusing on 1 particular item thus requires inhibition of irrelevant activity related to the processing of other items (Morey and Cowan 2005). Indeed, WM span and the ability to cope with interference are interindividually correlated (Long and Prat 2002), suggesting that similar processes are involved. On a neural level, both the resolution of conflict and manipulation of items in WM requires control processes within the anterior cingulate cortex (ACC), so that also the neural basis of these processes appears to be similar (e.g., Badre and Wagner 2004). It appears thus plausible that maintenance of multiple items in WM always involves some

degree of conflict processing, but that this is not a specific disadvantage of our design.

Is there any evidence that the subsequent forgetting effect in the PHC for DMS⁻ items is due to conflict processing? As described above, activity in the cingulate cortex, particularly the ACC, has been linked to conflict processing in various studies (for recent reviews, see Barch et al. 2001; Van Veen and Carter 2002). In our study, differential activation of the ACC was only observed in the DMS⁺LTM⁻ > DMS⁺LTM⁺ contrast (i.e., subsequent forgetting effect for items which have been successfully processed in WM; see Table 1), but not in those contrasts where activity in the PHC was observed (i.e., DMS⁺LTM⁺ > DMS⁻LTM⁻ and DMS⁻LTM⁻ > DMS⁻LTM⁺). Similarly, we did not observe significantly correlated activity between the PHC and the ACC in the connectivity analysis (Table 2). Although this is only an indirect argument, we are not aware of fMRI studies on conflict processing where activation of the ACC has *not* been reported.

Were our results confounded by the use of special strategies? A comparison with previous results suggests that this is unlikely: previous fMRI studies on subsequent memory effects of items which were successfully processed in DMS⁺ trials found effects in the PHC (Schon et al. 2004) and hippocampus (Ranganath, Cohen, et al. 2005), consistent with our findings. No previous data exist for DMS⁻ trials, because performance was close to ceiling in previous studies. Furthermore, we found that LTM performance was significantly better for DMS⁺ than DMS⁻ items both with (Fig. 2B) and without ($t_5 = 3.64$; $P < 0.01$) a surrounding Sternberg task, suggesting that interactions between DMS and LTM task are not seriously affected by the Sternberg task.

A better understanding of the dual role of PHC activation for memory formation requires to take into account both fMRI and electrophysiological data on this region. The PHC is 1 of several inferior temporal regions showing category-specific activation during visual perception (e.g., Logothetis and Sheinberg 1996; Tanaka 1996; Ishai et al. 1999). This activity may outlast stimulus presentation and is thus reminiscent of a neural correlate of content-specific short-term maintenance (Suzuki et al. 1997; Young et al. 1997), cooperating with item-unspecific WM regions such as the prefrontal cortex (Mecklinger et al. 2000; Fiebach et al. 2006). On the other hand, this region is linked to LTM encoding (e.g., Duzel et al. 2003), and activation of this region during WM facilitates subsequent LTM recognition (Schon et al. 2004; Ranganath, Cohen, et al. 2005). The facilitation of subsequent LTM formation by WM maintenance-related PHC activation has been explained by the necessity of a transient buffer during encoding (Atkinson and Shiffrin 1968; Baddeley 2000); indeed, similar regions are involved in content-specific perception and LTM (Khader et al. 2005). Computer models have suggested that stimulus-specific activity has to be maintained for some seconds before spike-timing dependent plasticity may occur (Jensen and Lisman 1996; Fransén et al. 2002). This is consistent with *in vitro* data showing that stimulation of the entorhinal cortex as part of the PHC activates muscarinic receptors which induce persistent spiking in entorhinal cells (Egorov et al. 2002). Taken together, these findings suggest that the PHC is well suited to support short-term maintenance of items by stimulus-specific sustained activity patterns, and that these activity patterns can be beneficial for LTM formation.

Interestingly, although computer simulations of persistent activity as a possible mechanisms of WM maintenance are based on very different mechanisms, they agree on the susceptibility of the model to become unstable (Wang 1999; Fransén et al. 2006). Indeed, a system involving strong reverberatory dynamics is likely to develop asynchronous population bursts involving a large proportion of all cells, as has been shown in the hippocampus (De la Prida et al. 2006). Thus, it is likely that the WM-related activity in the PHC can be easily disturbed. However, the successful encoding of items into LTM likely requires stimulus representations by highly selective subsets of neurons (Waydo et al. 2006) and precise temporal adjustment of neural spike patterns on a millisecond timescale (Fell et al. 2001; Herrmann et al. 2004). This suggests that activity in the PHC has to be meticulously controlled to be beneficial for the encoding of items into LTM, and that it can be detrimental for LTM formation otherwise. In addition, the interaction of WM and LTM processes (e.g., during reactivation of LTM traces in WM) has been suggested to rely on a complex interplay of oscillations in different frequency ranges, requiring precise temporal control of neural activity (Klimesch et al. 2005).

Increased activity which correlates with subsequent forgetting has been observed in a variety of regions including the posterior cingulate cortex (Otten and Rugg 2001) and dorsolateral prefrontal cortex (DLPFC; e.g., Clark and Wagner 2003). Daselaar et al. (2004) distinguished detrimental activation from beneficial deactivation and found that deactivation might as well be beneficial for memory formation. In our peristimulus time course analyses, we found evidence for both detrimental PHC activation above baseline level in the DMS⁻LTM⁻ condition and beneficial deactivation (below baseline) of this region in the DMS⁻LTM⁺ condition (Fig. 3B). The latter finding might indicate that highly selective stimulus representations in PHC are required for LTM encoding in the case of failure in the WM task.

Our analysis of functional connectivity revealed that activity within the PHC is correlated with extensive regions if both WM and LTM tasks are successfully solved, whereas the number of correlated voxels in the DMS⁻LTM⁻ condition was significantly reduced. Although the calculation of the number of correlated voxels (instead of the analysis of connectivity with specific regions) might be an unusual approach to analyze the data, we do believe that it is useful to address a relevant question in our study: because in the univariate analysis, BOLD responses in the PHC were similarly pronounced in the DMS⁺LTM⁺ and DMS⁻LTM⁻ conditions, we wondered whether the difference in task performance was related to the fact that parahippocampal activity in the DMS⁻LTM⁻ condition was correlated with fewer other regions (see above) as compared with the DMS⁺LTM⁺ condition. We aimed at testing this idea by comparing the number of correlated voxels in the different conditions. In principle, the correlation of more voxels with a seed region might indicate that activity in the seed region is not distinct from activity in other regions and may thus be functionally rather unspecific. On the other hand, integrated and successful processing in a seed region may actually depend on correlation of activity with activity in extended other regions. In the case of the PHC, we would rather predict the latter scenario, because activity in this region needs to be controlled meticulously to be beneficial for LTM formation and may otherwise even be detrimental (see above). The functionally connected regions during the correctly solved trials

resembled the regions described by Gazzaley et al. (2004) using a seed region in the right fusiform face area. Furthermore, distracter processing during a WM task has been shown to disrupt functional connectivity between inferior temporal and prefrontal areas (Yoon et al. 2006), directly supporting the functional relevance of connectivity for WM tasks. In addition to these effects of WM processing on functional connectivity, successful LTM formation has also been shown to enhance cortico-hippocampal interactions in both fMRI (Ranganath, Heller, et al. 2005) and intracranial EEG recordings (Fell et al. 2001).

In contrast to the findings from the univariate analysis, where PHC activity had opposite effects on subsequent memory during DMS⁺ and DMS⁻ trials, we found that subsequent memory was similarly correlated with an increased number of correlated voxels for both DMS⁺ and DMS⁻ items in the connectivity analysis. Thus, connectivity had similar effects on subsequent memory formation regardless of WM performance. Although this result may appear surprising given the different effects of PHC activity on LTM with and without successful WM performance in the univariate analysis, it suggests a possible neural basis for these different effects: similar activity patterns within the PHC during a WM task may have a different effect on LTM formation because they are correlated with activity in other brain regions during successful performance of the WM task, whereas they occur rather in isolation if the WM task is not executed successfully.

Does the different number of items in the different conditions contaminate our results? We argue that it is unlikely that the results from our univariate fMRI analyses are due to this difference: both the subsequent memory effect for DMS⁺ items and the subsequent forgetting effect for DMS⁻ items showed increased activation of the PHC, but the 1st contrast compared a condition with a larger number of trials to a condition with a smaller number of trials, whereas the 2nd contrast actually revealed increased activation for the condition with the smaller number of trials (26 as compared with 31). In the multivariate analysis, functional connectivity with the parahippocampal seed region seemed to decrease with the number of trials; to exclude the possibility that trial number actually contaminated results of this analysis, we ran an additional analysis where the variable trial number was corrected for by randomly selecting the same number of trials from each condition (Supplementary Fig. 2). Even though in this case a 2-way ANOVA with "DMS" and "LTM" as factors did not reach significance for "LTM" and the "DMS" × "LTM" interaction, the direct comparison between the number of correlated voxels in the DMS⁺LTM⁺ and the DMS⁻LTM⁻ condition was still significant. This comparison is particularly important because activity in the PHC was similarly enhanced during these 2 conditions in the univariate analysis, and the decrease in functional connectivity may thus explain the impaired performance during the DMS⁻LTM⁻ trials.

Taken together, our data provide evidence for an interaction of WM and LTM processes in the PHC. Although activity within this region is correlated with LTM formation for items which are successfully processed in a WM task, LTM encoding without successful WM performance is not supported by PHC activity. Further studies using high-resolution methods like intracranial electrophysiological recordings are required to characterize more closely the neural activity patterns which underlie different memory processes within this region.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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Notes

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Address correspondence to Dr Nikolai Axmacher, Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany. Email: nikolai.axmacher@ukb.uni-bonn.de.

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