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Research

Contributions of the medial temporal lobe to declarative memory retrieval: Manipulating the amount of contextual retrieval

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We investigated how the hippocampus and its adjacent mediotemporal structures contribute to contextual and noncontextual declarative memory retrieval by manipulating the amount of contextual information across two levels of the same contextual dimension in a source memory task. A first analysis identified medial temporal lobe (MTL) substructures mediating either contextual or noncontextual retrieval. A linearly weighted analysis elucidated which MTL substructures show a gradually increasing neural activity, depending on the amount of contextual information retrieved. A hippocampal engagement was found during both levels of source memory but not during item memory retrieval. The anterior MTL including the perirhinal cortex was only engaged during item memory retrieval by an activity decrease. Only the posterior parahippocampal cortex showed an activation increasing with the amount of contextual information retrieved. If one assumes a roughly linear relationship between the blood-oxygenation level-dependent (BOLD) signal and the associated cognitive process, our results suggest that the posterior parahippocampal cortex is involved in contextual retrieval on the basis of memory strength while the hippocampus processes representations of item-context binding. The anterior MTL including perirhinal cortex seems to be particularly engaged in familiarity-based item recognition. If one assumes departure from linearity, however, our results can also be explained by one-dimensional modulation of memory strength.

Declarative memory supports discrimination between previously encountered and novel stimuli by means of recollection and familiarity: While recollection involves recognition, including the retrieval of contextual information, familiarity refers to a feeling that a stimulus has been encountered previously without contextual retrieval (Mandler 1980).

Since Scoville and Milner (1957) reported their initial findings from patient HM, at least 50 years of converging evidence from human and animal lesion studies, as well as neuroimaging research, have identified the medial temporal lobe (MTL) as a crucial mediator of declarative memory (for recent reviews, see Diana et al. 2007; Eichenbaum et al. 2007). Based on cytoarchitecture and anatomical connectivity, MTL substructures in humans are dissociated into the hippocampus and the parahippocampal gyrus covered by the ento- and perirhinal cortex anteriorly, and the parahippocampal cortex posteriorly, which also extends into the medial regions of the fusiform gyrus (Insausti et al. 1987).

To date, the precise contribution of the hippocampus and the perirhinal and parahippocampal cortices remains a topic of debate: Based on behavioral data from patients with selective lesions of MTL substructures, one line of research proposes that the hippocampus is critical for recollection of episodic memories,

whereas the perirhinal cortex supports recognition judgments based upon familiarity (e.g., Brown and Aggleton 2001; Holdstock et al. 2005; Bowles et al. 2007; Sauvage et al. 2008). Another line of research does not support dichotomies between the functions of the hippocampus and the adjacent medial temporal structures, instead suggesting a functionally unified memory system within the MTL (e.g., Manns et al. 2003; Stark and Squire 2003; Wais et al. 2006; for a review, see Squire et al. 2004).

In recent years, functional magnetic resonance neuroimaging (fMRI) studies in healthy humans have gone beyond the natural limitations of lesion studies but have also generated controversial results. For example, while several studies report no difference between brain activity related to contextual and noncontextual memory retrieval within the MTL (e.g., Stark and Squire 2003; Kirwan and Stark 2004; Squire et al. 2004), other studies have revealed a dissociation between a hippocampal contribution to recollection (e.g., Eldridge et al. 2000; Yonelinas et al. 2001, 2005; Cansino et al. 2002; Giovanello et al. 2004; Weis et al. 2004a; Daselaar et al. 2006) and anterior MTL (most likely perirhinal) contributions to noncontextual item recognition based on familiarity (Henson et al. 2003, 2005; Weis et al. 2004a; Gonsalves et al. 2005; Daselaar et al. 2006; Montaldi et al. 2006).

Recently, the available evidence has been taken to suggest a dissociation between hippocampal and perirhinal functions and also the role of posterior parahippocampal cortex in declarative memory retrieval (Diana et al. 2007; Eichenbaum et al. 2007; see also Davachi 2006). Eichenbaum and colleagues (2007; see also Diana et al. 2007) suggested that perirhinal cortex is involved in

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familiarity-based representation of item information, while the posterior parahippocampal cortex is involved in representation of context, suggesting an important role in recollection. According to this model, the hippocampus integrates or binds the item and contextual information, and this will lead to reactivation of associated information in parahippocampal cortex during memory retrieval. Another perspective (Squire et al. 2007) suggests that different medial temporal processes are distinct but do not dissociate along the line between acontextual item memory and contextual–associative memory. In contrast, this perspective discusses a one-dimensional modulation of memory strength explaining differential behavior of MTL substructures. To explain functional imaging findings that do not show a monotonic change in activity paralleling monotonic changes in memory strength, Squire and colleagues (2007) propose a departure from linearity in the relationship between the blood-oxygenation level-dependent (BOLD) signal and memory strength in these MTL substructures.

Thus far, most of the studies have focused on contrasting one condition yielding contextual retrieval with another condition demanding simple recognition of item information (e.g., Eldridge et al. 2000; Cansino et al. 2002; Dobbins et al. 2003; Bunge et al. 2004; Giovanello et al. 2004; Weis et al. 2004a; Meltzer and Constable 2005). Such an approach is useful in dissociating the specific role of hippocampus and its adjacent mediotemporal structures in contextual and noncontextual forms of declarative memory. A complementary approach varies the amount of contextual information across several levels and allows us to investigate the neural response as a function of these levels as well as the sensitivity with which the different MTL structures react to the quantitative changes in the amount of contextual retrieval, thereby also taking into account the aspect of memory strength.

We, therefore, conducted an fMRI experiment, in which subjects were asked to remember photos of either landscapes or buildings that were dyed in different colors and different shades of these colors. In other words, the amount of contextual information was manipulated across two levels of the same contextual dimension (color) that were tested by means of a source memory task. We assumed that trials with mere item recognition reflect the least amount of contextual retrieval, trials in which retrieval of global source information (i.e., photos + color retrieval) was successful consist of an intermediate amount of contextual information, and trials in which two levels of source memory (i.e., photos + color + shade retrieval) were accomplished contain the greatest amount of contextual information. By comparing neural activity between trials reflecting successful source memory (collapsed over the two levels of contextual information) with trials reflecting simple recognition of previously presented stimuli as well as the latter ones with trials to previously presented but unrecognized stimuli (misses), we should be able to dissociate MTL activity mediating contextual and noncontextual retrieval as done previously. In particular, we were interested in whether all MTL subregions contribute equally to contextual- and non-

contextual memory retrieval or not. Based on the aforementioned hypotheses (Diana et al. 2007; Eichenbaum et al. 2007), we predicted that activation of the hippocampus and the posterior parahippocampal cortex co-occur during contextual retrieval, while anterior MTL regions (most probably within the perirhinal cortex) are selectively engaged in familiarity-based recognition. Additionally, our experimental design allowed us to test how activations change depending on the retrieval of different amounts of contextual information.

In addition, by contrasting trials of old items in a linearly weighted manner (i.e., unrecognized old items < recognized items < recognized items for which one level of source was correctly recollected < recognized items for which both levels of source were correctly recollected), we aimed to elucidate which MTL substructures responded in a gradually increasing or decreasing manner. FMRI activity in these substructures might thus reflect monotonically increasing or decreasing memory strength (Squire et al. 2007).

Results

Overall recognition was high (80.5%). The performance rate of correct judgments for "*2 source hits*," i.e., trials in which two levels of source memory (i.e., photos + color + shade retrieval) were accomplished ($t_{19} = 8.68$, $P < 0.001$), and "*1 source hits*," i.e., trials in which retrieval of global source information (i.e., photos + color retrieval) was successful ($t_{19} = 6.62$, $P < 0.001$), differed significantly from chance. There was a better performance for *1 source hits* in comparison with *2 source hits* ($t_{19} = 24.7$, $P < 0.001$), indicating that the latter one was more difficult to retrieve. For additional information also on the reaction times, see Table 1.

The global analysis (thresholded at $P = 0.001$; cluster-size test statistic, corrected for multiple nonindependent comparisons) confirmed previous findings (e.g., Weis et al. 2004a,b; Hornberger et al. 2006) of a significant difference between the neural activity for all recognized items versus misses, as well as in comparison to new items in mediotemporal, parietal, and prefrontal regions (for details, see Tables 2, 3). To delineate the involvement of the MTL substructures, a subsequent region of interest (ROI) analysis was performed within the MTL, as outlined in the Materials and Methods section (cf., Tendolkar et al. 2007).

By means of *t*-tests, we investigated whether there were any significant differences between hits with correct retrieval of context (collapsed over *1 source hits* and *2 source hits*) and hits without correct retrieval of context (*"item hits"*), as well as significant differences between hits with correct retrieval of context (collapsed over *1 source hits* and *2 source hits*) and correctly classified new items (*"correct rejections"*). We also included an analysis of activity decreases and increases between "*misses*" and *item hits* as well as *correct rejections* and *item hits* to further dissociate neural activity related to mere item recognition (Henson et al. 2003, 2005; Weis et al. 2004a; Gonsalves et al. 2005; Daselaar et al. 2006; Montaldi et al. 2006).

Table 1. Behavioral results

	Old items					New items		
	Uncertain	**Misses**	**2 source hits**	**1 source hits**	**Item hits**	**Uncertain**	**Correct rejection**	**False alarms**
% of trials[a]	6.2 ± 2.6	13.4 ± 3	23.6 ± 5	27.2 ± 4.2	29.6 ± 7.4	6.7 ± 2.1	72.8 ± 7.4	20.5 ± 4.5
No. of trials[b]	15 ± 6	32 ± 7	57 ± 12	65 ± 14	71 ± 18	8 ± 3	87 ± 9	25 ± 5
Reaction times[c]	2100 ± 440	2076 ± 443	1943 ± 411	2003 ± 434	2061 ± 474	2122 ± 484	1828 ± 381	1948 ± 355

[a]Mean percentage of trials (± standard deviation).
[b]Mean number of trials (± standard deviation).
[c]Mean reaction times (± standard deviation).

Table 2. Brain regions showing significantly greater BOLD signal ($P < 0.05$, corrected at the cluster level) during the overall analysis for recognized than for unrecognized stimuli during retrieval

Region	Left/right	No. of voxels/mm³	MNI coordinates			Z-value
			X	Y	Z	
Inferior frontal gyrus	Left	16,628/715,004	−44	4	30	6.4
Caudate nucleus	Left	2389/102,727	−12	10	0	6.04
Medial frontal gyrus	Left	152/6536	−24	32	−16	4.45
Parahippocampal gyrus	Right	38/1634	3	−26	−26	3.53

Second, we conducted an analysis testing how the activation pattern of the MTL substructures changes depending on the retrieval of different amounts of contextual information. The mean activation for all old items were taken and linearly weighted depending on the amount of contextual retrieval or memory strength that was associated with each condition (i.e., 2 source hits > 1 source hits > item hits > misses).

Below we will report the results of these analyses arranged by MTL substructures.

Hippocampus

The first analysis showed a larger hippocampal activity (cluster size: 20 voxels/860 mm³) for hits with correct contextual retrieval (collapsed over *1 source hits* and *2 source hits*) compared with those without (*item hits*) with local maxima in the middle (−28, −26, −10; $P_{corr} < 0.01$) and the dorsal aspect of the left hippocampus (−30, −38, 0; $P_{corr} < 0.01$) (Fig. 1A). In order to dissociate the hippocampal activity that was selectively engaged by either of the two source memory conditions, we compared directly *1 source hits* and *2 source hits*. While the comparison *2 source hits* versus *1 source hits* gave rise to a larger activation in the left middle/anterior hippocampus (cluster size: 8 voxels/344 mm³; −24, −28, −10; $P_{corr} < 0.001$), *1 source hits* versus *2 source hits* did not reveal any significant hippocampal activation (Fig. 2). Moreover, no hippocampal activation was found for noncontextual memory when comparing *item hits* with either *misses* or *correct rejections*. Finally, the linearly weighted analysis did not show any significant effects within the hippocampus.

Anterior MTL

In a region of anterior MTL (Fig. 1B), which includes the perirhinal cortex, the first analysis gave rise to a decrease of activity for *item hits* opposed to *misses* (cluster size: 6 voxels/258 mm³; 24, −2, −30; $P_{corr} < 0.05$) and opposed to *correct rejections* (cluster size: 5 voxels/215 mm³; 28, 0, −26; $P_{corr} < 0.05$). None of the other contrasts as outlined previously showed any significant effects within this region.

Posterior parahippocampal cortex

Analyses revealed no significant activations when contrasting hits with correct retrieval of context (collapsed over *1 source hits* and *2 source hits*) to those without (*item hits*) as well as correctly classified new items (*correct rejections*). There was significantly more activity for *item hits* compared with *misses* in left fusiform

gyrus most probably covered by parahippocampal cortex (cluster size: 9 voxels/387 mm³; −32, −42, −20; $P_{corr} < 0.05$). However, no significant difference between *item hits* and *correct rejections* were found. Finally, the linearly weighted analysis (i.e., 2 source hits > 1 source hits > item hits > misses) showed significant effects within the left (cluster size: 10 voxels/430 mm³; −20, −44, −6; $P_{corr} < 0.01$) and the right posterior parahippocampal cortex (cluster size: 18 voxels/774 mm³; 24, −56, −2; $P_{corr} < 0.05$). Indeed, the bar graphs in Figure 1C depicting the contrast estimates show the graded nature of this memory effect.

Discussion

In this study, we investigated how the hippocampus and its adjacent mediotemporal cortices contribute to contextual and noncontextual forms of declarative memory retrieval. A hippocampal engagement could only be identified during contextual-memory retrieval, while activity in anterior MTL was only found in the form of an activity decrease related to noncontextual item recognition. Posterior parahippocampal cortex showed an activation gradually increasing with the amount of contextual information retrieved.

First, our results replicate earlier fMRI studies showing a selective engagement of the hippocampus in contextual memory retrieval (Eldridge et al. 2000; Cansino et al. 2002; Giovanello et al. 2004; Weis et al. 2004a; Daselaar et al. 2006; for review, see Eichenbaum et al. 2007), thereby supporting a specific role for the hippocampus in recollective aspects of declarative memory (Brown and Aggleton 2001; Eichenbaum and Cohen 2001; O'Reilly and Norman 2002). Moreover, recollection of both levels of source memory compared with just one level resulted in a more anterior extension of the hippocampal activation. In this context, we note that the hippocampus receives input originating from diverse neocortical regions. The neocortex and the hippocampus are indirectly connected via the parahippocampal gyrus, whereby anterior neocortical regions connect to the anterior parahippocampal cortex, and whereby posterior neocortical regions connect to the posterior parahippocampal cortex (Insausti et al. 1987; Suzuki and Amaral 1994). The increase of activation pattern along the longitudinal axis of the hippocampus in our study might thus reflect an increase in hippocampal input related to the retrieval of additional contextual information from different neocortical sites. However, it is rather unlikely that color and shade of a color induce different neocortical representations. Hence, it is more likely that the extension of hippocam-
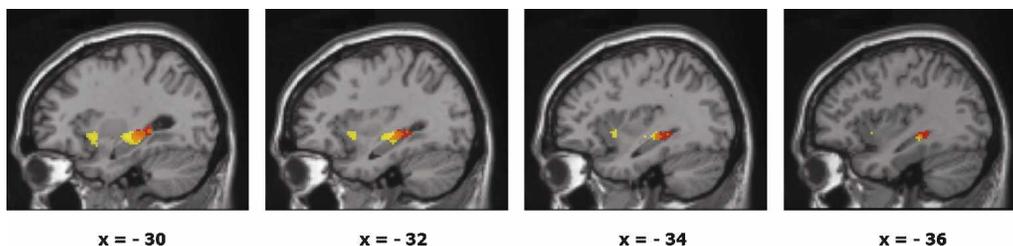
Table 3. Brain regions showing significantly greater BOLD signal ($P < 0.05$, corrected at the cluster level) during the overall analysis for recognized than for correctly rejected new stimuli during retrieval

Region	Left/right	No. of voxels/mm³	MNI coordinates			Z-value
			X	Y	Z	
Supplementary motor area	Left	6844/294,292	−4	10	52	7.5
Inferior parietal gyrus	Left	2912/125,216	−28	−62	42	6.5
Precuneus	Left	921/39,603	−8	−68	54	5.4
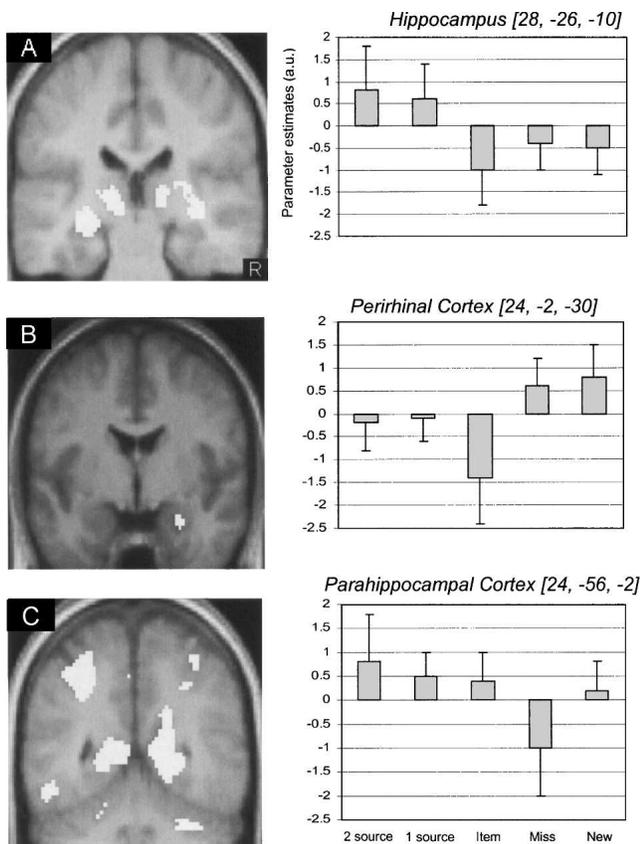
Figure 1. Specific activations from the ROI analyses within the MTL ($P_{corrected} < 0.05$, thresholded at a voxel size of 10) of the hippocampus (*A*), right anterior MTL (*B*), and left and right posterior parahippocampal cortex (*C*) are shown superimposed onto selected coronal slices of the mean high-resolution T1-weighted volume supplied with SPM2. R refers to the right side of the brain. The bar graphs show the corresponding contrast estimates derived from the local maxima of the ROI analyses. The hippocampal activation (*A*) reflects the stepwise contrast between hits with correct contextual retrieval (collapsed over 1 source hits and 2 source hits) compared with those without (item hits), while the anterior MTL effect with a local maximum in perirhinal cortex (*B*) reflects the significant signal decrease of merely recognized stimuli (item hits) compared with misses and correct rejections. Finally, the posterior parahippocampal activation (*C*) results from a linear trend analysis reflecting the different amount of contextual retrieval across all four conditions (2 source hits, 1source hits, item hits, misses) of previously presented stimuli as outlined in the Materials and Methods section.

pal activations along its longitudinal axis reflect an increase in "intrinsic" hippocampal information processing related to the retrieval of more binding or associations between the picture and

its color context. As our data contain the same kind of contextual information, color, these do not speak to the question of whether the posterior or anterior parts of the hippocampus in healthy humans may be responsible for dissociable functions in contextual retrieval (Moser and Moser 1998).

The observed activation of posterior parahippocampal cortex in relation to contextual memory retrieval is also in line with several other studies (e.g., Cansino et al. 2002; Kirwan and Stark 2004; Yonelinas et al. 2005, Hayes et al. 2007). Our findings extend previous results in that we show that activation of posterior parahippocampal cortex increased as a function of the amount of contextual information that had to be reactivated for successful retrieval. Given that color and shade of color represent two features of the same contextual dimension, the gradual increase in parahippocampal cortex can best be interpreted as a parahippocampal process contributing to the reactivation of actual contextual representations during retrieval. Thus, our data are in line with the hypothesis that the posterior parahippocampal cortex contributes to the recollection of contextual information (Diana et al. 2007; Eichenbaum et al. 2007).

However, we found a monotonic increase in activity from *misses* over *item hits* and *1 source hits* to *2 source hits* in the parahippocampal cortex (Fig. 1C). Appreciating the results as depicted in Figure 1 and described in the Results section suggests that the monotonic increase of parahippocampal activation is driven by an increase in contextual retrieval or memory strength (Squire et al. 2007). Our data cannot discern between these two interpretations for the posterior parahippocampal activation pattern found. Note that during the memory encoding part of this study (Tendolkar et al. 2007), posterior parahippocampal activation was also found, which increased with the amount of contextual information to be encoded. Hence, converging the data from encoding and retrieval supports the idea that posterior parahippocampal cortex might be involved in both encoding and retrieval in a way that is related to memory strength or the amount of contextual information encoded/retrieved.

The hippocampal activation pattern (Fig. 1A) shows quite distinctive responses for trials with and without source retrieval, indicating a specific role in associative retrieval of source information. The pattern of hippocampal activation might also be in line with a memory strength interpretation, but only if one assumes a nonlinear relationship between the BOLD signal and memory strength as suggested by Squire and colleagues in their recent review (Squire et al. 2007). Such departure from linearity may make a dissociation of hippocampal responses to item hits and misses potentially impossible.

Finally, we found less perirhinal activity for successful item recognition compared with trials in which recognition failed or was correctly rejected as being new. Such a decrease in activity related to successful item recognition has previously been explained by a model in which new or unfamiliar items require

Figure 2. Displayed are the results from the stepwise *t*-tests ($P_{corrected} < 0.05$, thresholded at a voxel size of 10) for 2 source hits versus item hits (shown in yellow) and 1 source hits versus item hits (shown in red). The activations are displayed on sagittal slices of the standard T1-weighted volume supplied with SPM2. The activation shown in orange reflects the results from a conjunctional analysis (thresholded at $P < 0.001$ uncorrected) between the hippocampal activation for 1 source hits and 2 source hits superimposed on the aforementioned stepwise analysis.

more neural resources than familiar items (Henson et al. 2003, 2005; Weis et al. 2004a; Gonsalves et al. 2005; Daselaar et al. 2006; Montaldi et al. 2006; Hornberger et al. 2006). However, such findings have also been interpreted as being in line with a memory strength account by assuming nonlinearity in the relationship between the BOLD signal and memory strength (Squire et al. 2007). Indeed, we found that activity in the same region during memory formation increased as a function of the amount of information that was encoded (Tendolkar et al. 2007). Thus, the increase for misses during retrieval could also mean that the items might be treated as new and therefore generate encoding related activity. In other words, retrieval and encoding related activity in this MTL region might represent a correlate of the very same process, starting to encode new information and diminishing encoding when a familiarity signal is present (Fernández and Tendolkar 2006).

As discussed, the interpretation of our data hinges significantly on the assumption that there is either a linear or nonlinear relationship between the BOLD signal and the cognitive process at issue. If one assumes linearity, the parahippocampal response might be readily linked to the amount of associative information retrieved or the associated memory strength. However, perirhinal and hippocampal response patterns under this assumption more easily explained by a process dissociation between distinct processes linked either to item or associative memory. Contrary, if one assumes nonlinear process-BOLD functions with different characteristics in different MTL substructures, all our results can be interpreted as in line with a memory strength account. Several studies have shown linear relations between neural activity and associated BOLD responses in a wide range of regions, but nonlinear components occur at the extremes and these nonlinearities appear to be different in different brain structures (e.g., Boynton et al. 1996; Soltysik et al. 2004). Although there is no good reason to assume different nonlinear functions within the MTL, there is, to the best of our knowledge, no study confirming the linearity of the neural-BOLD coupling in the MTL. Hence, we cannot exclude this alternative interpretation currently.

In summary, as long as one assumes linearity between the BOLD signal and the associated cognitive process, our results suggest that the posterior parahippocampal cortex is involved in contextual retrieval, potentially on the basis of memory strength, while the hippocampus processes representations of item-context binding. The anterior MTL including the perirhinal cortex seems to be particularly engaged in familiarity-based item recognition.

Materials and Methods

After giving informed consent, 20 healthy, right-handed subjects (10 females; mean age 25 yr, range 18–36) participated in the experiment, which was performed according to the guidelines provided by the local medical ethics committee. The experiment consisted of five study-test cycles, whereby every four subjects saw the same set of five study-test cycles. As stimuli, 360 grayscale photographs of natural landscapes with or without buildings were randomly divided into five sets of pictures, 36 with and 36 without buildings. During the study, stimuli were colored in a light, lurid, and dark shade of red or green. During testing, stimuli were shown in grayscale (for an overview of the experimental set-up, see Fig. 3).

During each of the study phases, 48 photographs were displayed for 1400 msec, followed by a fixation point appearing for 2400–3700 msec. Following each photograph, a screen with the three different shades of either red or green squares (depending on the color of the antecedent picture) (Fig. 3) appeared for 1200 msec. During each of the test phases, the 48 old photographs were presented intermixed with 24 new ones, each for 1400 msec, followed by a jittered fixation period between 2400–3700 msec. To optimize the event sequence for statistical analysis, jittering of the interstimulus interval was done as indicated before, and 24 null-events (black screen with a fixation point in the middle for 2000 msec) during study and 36 null-events during tests were intermixed.

At study, subjects memorized each picture together with its color/shade by making a landscape/building (covertly) and a color/shade-decision (button press). During retrieval, the subjects were required to indicate by a button press whether the displayed photograph either was not seen before ("new") or was seen at study and previously presented in red ("old previously red") or green ("old previously green"). After a "new" judgment, no further action was required for this particular item. If the subject classified the photograph to be old previously red or old previously green, three color-cues with the three different shades of either red or green were shown, and subjects were required to decide in which shade the photograph had been presented during the study phase (see Fig. 3). In keeping with previous studies (Weis et al. 2004 a,b), for old/new and shade decisions, subjects could make use of an "uncertain" response in order to avoid a contamination by guesses. The use of the left or right hand for button presses was counterbalanced across subjects. Before scanning, a practice session was given to the participant to ensure that the subject was familiar with the entire procedure in the scanner.

Functional MR volumes were acquired with an ascending slice-acquisition T2*-weighted echo-planar imaging sequence
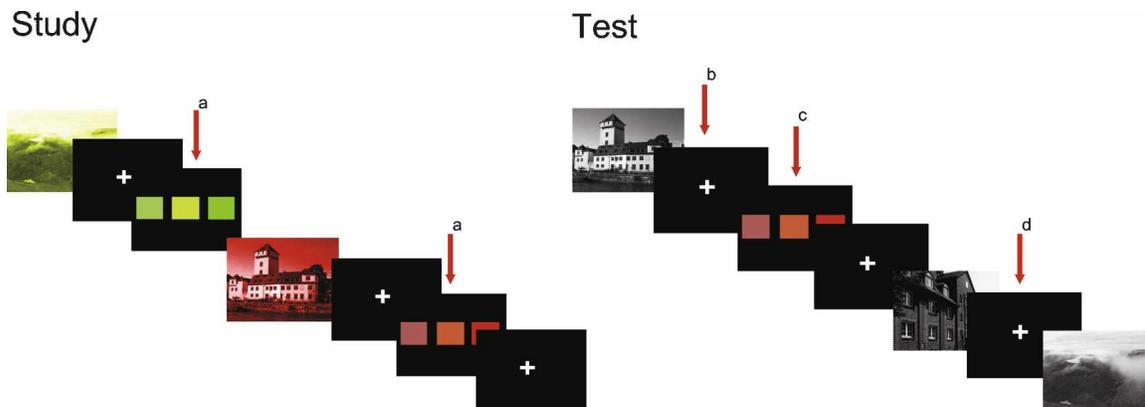
Figure 3. Simplified depiction of study and test trials. The letters a–d indicate whenever a button press had to be made. At a, subjects were required to indicate during study which color and shade of the color the pictures were dyed in. At b, subjects judged by button presses whether the photo was previously presented in red (old, previously red) or in green (old, previously green). If the subject judged the photograph to be old, previously red or old, previously green, subjects were required to indicate, at c, in which shade the photograph had been presented during the study phase. At d, subjects were required to press the button if they had not seen the photo before (new).

(Sonata 1.5 T, Siemens; 33 axial slices; volume repetition time [TR] = 2.29 sec; echo time [TE] = 30 msec; 90° flip angle; slice matrix = 64 × 64; slice thickness = 3.0 mm; slice gap = 0.5 mm; isotropic voxel size = 3.5 × 3.5 × 3.5 mm^3; field of view = 224 mm) during encoding and retrieval of the present experiment. A T1-weighted MP-RAGE sequence (176 sagittal slices; volume TR = 2250 msec; TE = 3.93 msec; 15° flip angle; slice matrix = 256 × 256; slice thickness = 1.0 mm; no gap; field of isotropic voxel size = 1 × 1 × 1 mm^3; view = 256 mm) was acquired for anatomical localization.

Analysis was performed using SPM2 (Friston et al. 1995, 1996; www.fil.ion.ucl.ac.uk/spm). After discarding the first five volumes in every session to allow for T1 equilibration effects, the functional EPI-BOLD images were realigned, and the subject means were coregistered with the corresponding structural MR images using mutual information optimization. Volumes were subsequently slice-time corrected and then normalized to the stereotactic anatomical MNI space. Data were smoothed with an isotropic three-dimensional Gaussian kernel (8-mm FWHM). The fMRI data were analyzed statistically using the general linear model. The explanatory variables were temporally convolved with the canonical hemodynamic response function provided by SPM2. In addition, the linear model included a temporal high-pass filter to account for various low-frequency effects and re-alignment parameters as effects of no interest. Relevant contrast parameter images were generated for each subject on the basis of the following test trials: (1) recognized old items, for which the correct color and shade was retrieved (*2 source hits*); (2) recognized items, for which only the correct color was retrieved (*1 source hits*); (3) recognized items without correct retrieval of contextual information (*item hits*); (4) old items misclassified as new *(misses)*; and (5) correctly classified new items (*correct rejections*). Trial types 1, 2, and 3 were combined as "*overall hits.*" These contrasts were subsequently subjected to a second-level random effects analysis as outlined in the Results section. Note that the main purpose of this study was to dissociate MTL activity related to contextual and noncontextual memory retrieval so that a global analysis over the whole brain was only taken as a confirmation of significant activations that have been previously associated with contextual and noncontextual forms of recognition memory using a similar experimental set-up (Weis et al. 2004a,b). Therefore, we compared neural activity between all recognized items and misses as well as neural activity between all recognized items and new items over the whole brain thresholded at $P = 0.001$. In this analysis, the cluster size, corrected for multiple nonindependent comparisons, was used as test statistic. To delineate the involvement of the MTL substructures, a subsequent region of interest (ROI) analysis was performed within the MTL using two anatomically defined mask-images generated for both left and right MTL (including hippocampus and parahippocampal and fusiform gyrus) based on the Talairach Daemon database (Maldjian et al. 2003). All P-values reported were corrected for multiple nonindependent comparisons (small volume correction based on the family-wise error). We report MNI $X/Y/Z$ coordinates of local maxima together with the voxel and corresponding volumina size of the significant cluster.

Two kinds of ROI analyses were performed within the MTL. In the first analysis, we analyzed by means of *t*-tests whether there were any significant differences between hits with correct retrieval of context (collapsed over *1 source hits* and *2 source hits*) and hits without correct retrieval of context *(item hits)* as well as significant differences between hits with correct retrieval of context (collapsed over *1 source hits* and *2 source hits*) and correctly classified new items (*correct rejections*). This analysis also included a comparison of activity decrease and increase between *misses* and *item hits* to further dissociate neural activity related to mere item recognition (Henson et al. 2003, 2005; Weis et al. 2004a; Gonsalves et al. 2005; Daselaar et al. 2006; Montaldi et al. 2006).

Second, we conducted a linearly weighted analysis investigating how the activation pattern of MTL substructures changes as a function of memory strength across the different conditions of previously presented stimuli, assuming that correctly recognized items for which the two contextual details could be recalled, yielded the strongest memory while *misses* should yield the weakest memory.

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