

Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study

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The temporal lobe regions involved in memory retrieval were examined using fMRI. During an associative recognition test, participants made memory judgments about the study color of previously presented drawings of objects, and during item recognition tests they made old/new judgments about previously studied objects or new objects. Associative recognition compared with old item recognition led to activations in bilateral hippocampal and parahippocampal regions, as well as

in the left middle occipital gyrus. Old item recognition compared with new item recognition led to activation in the left middle occipital gyrus and the left middle temporal gyrus, and relative deactivations in bilateral hippocampal regions. The results indicate that partially distinct temporal lobe regions are involved during recognition memory for item and associative information. *NeuroReport* 12:359–363 © 2001 Lippincott Williams & Wilkins.

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INTRODUCTION

Several regions within the temporal lobes are involved in human recognition memory. It is not yet clear, however, what specific mnemonic functions these various regions support. Evidence from lesion and electrophysiological studies of rats and non-human primates suggests that the hippocampal region is necessary for recollection, the retrieval of arbitrary associations between different aspects of an event, whereas other temporal lobe regions, such as the parahippocampal and perirhinal regions, do not readily support memory for arbitrary associations, although they can support discriminations between recently presented (i.e. familiar) items and new items [1,2]. Although the evidence for such a functional-anatomical distinction in humans is less compelling, the existing evidence suggests that a similar distinction may be observed in humans. For example, patients with damage restricted primarily to the hippocampal region exhibit severe deficits on tests that require recollection, such as free recall, but perform relatively normally on single item recognition tests that could be based on familiarity assessment or the retrieval of non-associative information [3]. Furthermore, patients with more extensive temporal lobe lesions (extending beyond the hippocampus), exhibit deficits in familiarity as well as in recollection [4].

In the current study we used functional magnetic

resonance imaging (fMRI) to examine the contributions of the temporal lobes to associative recognition memory and to single item recognition memory. Specifically, medial temporal lobe regions (the hippocampus, the entorhinal and parahippocampal gyri), and adjacent occipital-temporal regions (the fusiform, inferior temporal, posterior middle temporal, and middle occipital gyri) were the main focus of this study, based upon the results of previous imaging studies that showed the importance of these temporal lobe regions to memory retrieval [5–7]. Participants were scanned in three different memory test conditions. One condition, the associative recognition condition, was designed to optimize the involvement of recollection and familiarity. For each test item, participants were required to indicate which color the item was presented in during an earlier study phase. If participants were able to accurately retrieve the arbitrary item-color association, the regions supporting recollection should be activated in this condition. Moreover, because all the items were previously studied, they should also be familiar, and thus regions involved in familiarity should also be activated. A second condition, the old item recognition condition was designed to optimize the likelihood of familiarity based recognition while minimizing recollection. Participants were required to discriminate between familiar and new drawings of objects. During the OLD item condition, the test list

consisted of items that were recently studied under conditions in which participants attended to the perceptual aspects of each item, conditions that have been shown to optimize familiarity [8–11]. A third condition, the new item condition was designed to minimize the likelihood of recollection and familiarity. The new item condition was identical to the old item condition except that the test list contained only new items, and thus both recollection and familiarity were expected to be minimal.

Direct comparisons across the three conditions were used to separate activations related to recollection of associative information and item familiarity. The associative test optimized both recollection and familiarity, and the old test optimized familiarity but minimized recollection, thus regions associated with recollection should be significantly more active in the associative condition than the old condition. In contrast, because the old item condition optimized familiarity, and the new item condition minimized familiarity, regions associated with familiarity should be more active during the old condition than the new condition.

MATERIALS AND METHODS

Participants and materials: Six healthy right-handed college-aged (ages 20–34; four female) participants were paid \$15/h. The experiments were conducted with the understanding and signed consent of each participant and the experiment was approved by the Human Subjects Committee at the University of California, Davis. Three hundred and sixty images (drawings and silhouettes of clip-art objects from MasterClips, 1998) served as study and test items. Items were randomly assigned to the associative (144 items) and recognition (216 items) memory conditions. Items were presented in monochrome on a white background. All items were presented in black, except that half of the items in the associative study list (randomly selected) were presented in red and half were presented in green.

Procedures: One day prior to scanning subjects studied 144 clip-art images. Half of the images were presented in red and half were presented in green, and participants were instructed to remember the presentation color of each image. In order to facilitate later recollection of the association between the item and its color, participants were required to generate an explanation for why the object was presented in that particular color. Moreover, immediately after the study list, participants were presented with an associative memory test in which all the studied items were presented in black and participants indicated which color had been used in the original presentation. Participants received immediate feedback on each item.

Immediately prior to scanning, participants were given practice performing the memory tasks to ensure that they understood the instructions, and they also completed a study task, the details of which are described below, to familiarize them with the items in the old item recognition test. Participants were placed in the MRI scanner and fitted with a headcoil-mounted bite-bar that was used for head stabilization. Stimuli were projected onto a back-projection screen located at the end of the MRI gantry that was viewed by means of a mirror inset into the scanner head

coil. Participants responded by pressing one of two fiber-optic mouse buttons using the index and forefinger of their right hand.

Each participant received six 288 s scans. The first 32 s of each scan were discarded (to allow for saturation effects) and no stimuli were presented during this period. There were two scans for each of the associative, old, and new conditions, and these were presented in a counterbalanced order across subjects. In each of the scans, a blocked design was used such that the experimental condition was alternated with a control condition (16 s of the associative experimental condition, 16 s of the control task, 16 s of the associative experimental condition, etc.). The control condition consisted of a central fixation cross with one shape presented on either side of the cross (circles and squares). The participant pressed a switch to indicate whether the left or right figure was larger. This condition was used to control for motor responses, and to control the behavior of the participant during the "off" condition. That is, to ensure that participants did not continue to retrieve either memories of the objects that were just seen or other self-generated memories. The stimulus presentation rate in the experimental and control conditions was 2.667 s per trial (the target stimuli were presented for 1200 ms followed by 1467 ms of blank screen). Across the experiment, each participant received 96 test trials (i.e. test items) in each of the three experimental conditions.

In the experimental condition of the associative test, black images of objects were presented, and participants indicated the original study color of the item by pressing one of two switches (i.e. index finger if it was red and forefinger if it was green). All of the items were previously studied in either red or green and participants were instructed to make a response for each item, guessing if they were unsure.

In the old and new test conditions, participants were first presented with a study list in which 120 black and white images of objects were presented. Each item was presented for 500 ms followed by 500 ms of blank screen, and participants pressed one switch if the picture was a silhouette, and another if it was a line drawing. Note that participants had performed this study task one time just before entering the MRI scanner. In the old test condition, participants were then scanned while they made recognition memory judgments. They were presented with a list that consisted of items that were from the preceding study list, and they responded with the index finger if they thought the item was studied, and with the forefinger if they thought it was not studied. In order to maximize the occurrence of familiarity in this condition, and to match the design of the associative condition, all of the test items in the old test condition were studied. However, participants were told that most, but not all, of the items were from the previous study list, in order to ensure that they continued to engage in memory retrieval attempts for each item in the list. The new test condition was identical except that all of the items were new to the experiment, and participants were informed that most, but not all, were new.

Immediately after the scanning session was complete, participants were given a final recognition test containing 48 items from the associative study list, 48 items from the

old study list, and 96 new items mixed in a random order. None of these items were used during the scanning test conditions. For each item, participants indicated if it was studied earlier, and, if it was studied, if they could remember any qualitative information about the study episode [12]. The remember responses were collected in order to verify that the probability of recollection was greater for the items in the associative condition than the items in the old condition.

MRI acquisition and analysis: The scans were conducted using a 1.5 Tesla GE CV/I MRI System (GE Medical Systems, Waukesha, WI). Each session included a sagittal T-1 weighted localizer scan, a high resolution proton density and T2-weighted oblique coronal fast spin echo scan, and an IR-prepped 3-D T1 weighted oblique coronal SPGR scan. Functional images were acquired using T2* weighted gradient-recalled echo, single-shot echo planar imaging (EPI; 16 slices, 4mm thick with 1mm interslice gaps, 64 × 64 matrix; FOV = 22 cm, TR = 2000 ms, TE = 32 ms, FA = 90°). For each TR, 20 interleaved EPI images were collected as oblique coronal slices, oriented perpendicular to the hippocampal axis with the most anterior slice aligned with the anterior edge of the amygdala. In each functional scan, 144 images were acquired at each slice location, for a total acquisition time of 288 s (4 min 48 s).

After data acquisition, Fourier image reconstruction was performed, including N/2 ghost correction using image phase correction [13]. The EPI images were then realigned and corrected for movement artifacts. The subjects' scans were spatially normalized to the standardized stereotactic space defined by the Montreal Neurological Institute's (MNI) template brain using the template and routines provided in SPM99 (Wellcome Department of Cognitive Neurology). The EPI images were spatially smoothed with an 8 mm isotropic Gaussian kernel.

The analyses were performed by convolving the box-car function that represents the alternation of the experimental and control tasks (16 s on/16 s off cycles) with a synthetic hemodynamic response function to create a model response function (which included a temporal derivative). The data were smoothed with an 8 s full width at half maximum Gaussian kernel to account for temporal auto-

correlations in the time-series data before the analyses were performed. Low frequency drifts were modeled and filtered using a high-pass filter cutoff of 68 s within each session. A multiple regression analysis was then conducted using SPM99 to identify voxels in which the variations in the BOLD signal were modeled well by the alternations in experimental conditions.

Planned contrasts were then performed to investigate the temporal lobe regions that showed differential activity in the three different experimental conditions relative to the control task, as described above. Statistical analyses were performed separately at each voxel. For the medial temporal and occipital-temporal regions that were our a priori regions of interest, uncorrected *p* values of < 0.001 were utilized to provide the most sensitive analyses in these critical regions. Analyses of the brain areas outside of our regions of interest are not reported here.

RESULTS

Recognition accuracy levels were high in all the experimental conditions (i.e. 0.89, 0.85 and 0.95 for the associative, old, and new item conditions, respectively) indicating that the brain activation being measured was associated with successful memory performance. Moreover, the accuracy levels were comparable in the three conditions (*p* > 0.1) suggesting that, the conditions were roughly equated in terms of task difficulty during the scanning sessions. The final recognition test, administered after all scanning sessions were complete, revealed that the proportion of 'remember' responses (to items that had been studied, but that had not been in the testing sessions) was greater for items studied for the associative test (0.99) than for the items studied for the old item recognition test (0.58, *p* < 0.001). These results indicate that our encoding manipulations were successful in leading to greater recollection in the associative condition than the old condition.

Associative vs old item recognition: A comparison of activations in the associative recognition condition to the old item recognition condition indicated that bilateral hippocampal and parahippocampal regions were significantly more active during associative recognition than during old item recognition (Table 1). Figure 1a illustrates

Table 1. Maxima within the medial temporal and occipital-temporal regions of interest showing significant (*p* < 0.001 uncorrected) BOLD signal changes.

	Talairach coordinates			t-value	Label in Figure 1
	x	y	z		
Associatives > old item recognition					
L hippocampal	-24	-21	-18	4.86	H
R hippocampal	24	-21	-18	3.79	
L parahippocampal	-33	-39	-12	7.18	P
R parahippocampal	33	-33	-18	4.44	
L middle occipital gyrus	-51	-69	-9	5.01	
Old > new item recognition					
L middle occipital gyrus	-51	-63	-9	4.36	O
L middle temporal gyrus	-54	-45	-9	3.72	T
New > old item recognition					
L hippocampal	-24	-21	-10	3.41	H
R hippocampal	24	-18	-18	3.19	

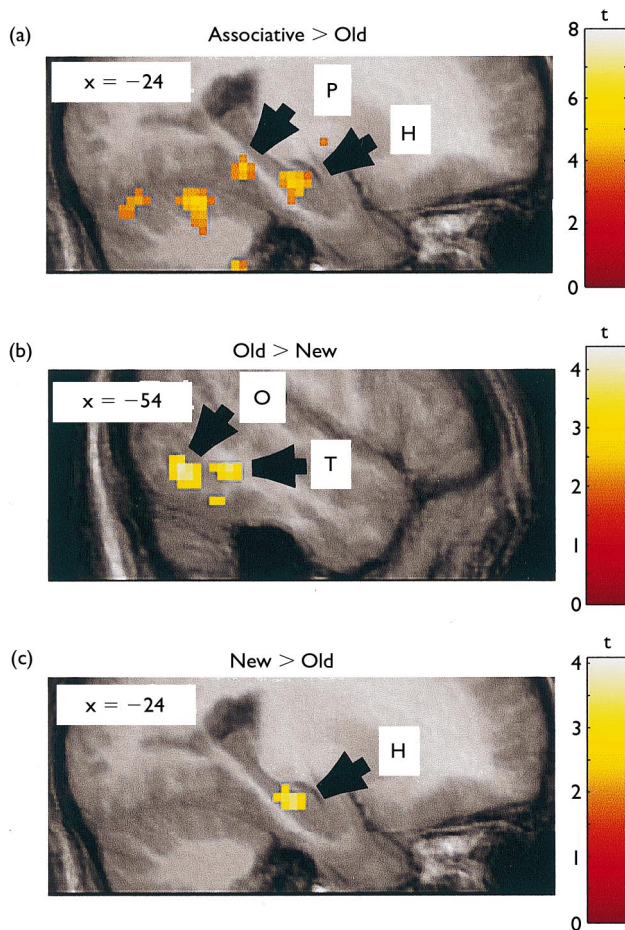


Fig. 1. Regions of activation overlaid on the average normalized T1 structural images. (a) Bilateral hippocampal (H) and parahippocampal (P) regions were more active during associative recognition than old item recognition (the left hemisphere activations are shown here). (b) Regions in the left middle occipital gyrus (O) and left middle temporal gyrus (T) were more active for old than for item recognition. (c) Bilateral hippocampal (H) regions were more active for new item recognition than old item recognition (the left hemisphere activation is shown here). For illustrative purposes an uncorrected threshold of $p < 0.0001$ was used in (a), and $p < 0.005$ was used in (b) and (c).

the average hippocampal and parahippocampal activation associated with the associative compared to the old condition overlaid on the average structural MR of the 6 subjects. The hippocampal activation involved the hippocampus proper, subiculum, entorhinal cortex and extended into the medial parahippocampal gyrus. The parahippocampal activation included the posterior portion of the parahippocampal gyrus along the collateral sulcus where it extended into the fusiform gyrus. An area in the left occipital-temporal region (middle occipital gyrus) was also significantly more active during associative than old item recognition (Table 1). No other significant activations or deactivations were observed in this comparison in the regions of interest.

Old vs new item recognition: A comparison of the old and new item recognition conditions indicated that two regions in the left occipital-temporal region (the middle

occipital gyrus and the middle temporal gyrus) were significantly more active during old than new item recognition (Table 1, Fig. 1b). The location of the middle occipital gyrus activation overlapped with the middle occipital gyrus activation observed in the associative *vs* old item comparison. No other significant activations were observed in any of the regions of interests. However, a relative deactivation in the old compared with new item recognition conditions (i.e. significantly more activation for the recognition of new than of old items) was observed in bilateral hippocampal regions (Fig. 1c). The location of the hippocampal deactivations overlapped with the hippocampal regions that were active in the associative rather than old item conditions, but they were less extensive than those seen in the associative memory comparison.

DISCUSSION

The current study examined the temporal lobe regions that were involved with associative and item recognition for previously studied drawings of objects. Associative recognition memory for object-color relationships, compared with item recognition for studied objects, led to bilateral hippocampal and parahippocampal activation, as well as activation in the left middle occipital gyrus, suggesting that recollection was subserved by these three temporal lobe regions. In contrast, item recognition of studied objects, compared to recognition of new objects, did not lead to increased hippocampal or parahippocampal activation; rather it was associated with activation in the left middle temporal gyrus and the left middle occipital gyrus, suggesting that retrieval of item familiarity relied on occipital-temporal regions rather than on hippocampal or parahippocampal regions.

Several previous imaging studies have indicated that the temporal lobes are involved in successful recognition memory, but it has not been clear from those results whether these regions are involved in the recollection of associative information or the detection of item familiarity. For example, hippocampal and parahippocampal activation has been observed for old *vs* new items during recognition memory tests [14,15], for well recognized *vs* poorly recognized items [16], and for items associated with 'remember' responses compared to those judged to be new [17]. However, the observed activations in these studies could reflect differences in either recollection or familiarity between the two types of test items contrasted. The current results indicated that hippocampal and parahippocampal regions were involved in associative recollection, and the results provided no evidence that these regions were involved in item familiarity.

The hippocampal activation related to associative rather than old item recognition is consistent with models that postulate that the hippocampal region is necessary for recollection of associative information whereas other temporal lobe regions are necessary for assessment of item familiarity [1,2]. However, other aspects of the current results are not predicted by these models. For example, these models assume that the parahippocampal region is involved in item recognition. In contrast, the item recognition comparison led to activation of occipital-temporal regions rather than the parahippocampal region, whereas associative memory activations included parahippocampal

and occipital-temporal regions as well as hippocampal regions. Although further studies are needed to determine the precise roles of these regions, one speculation is that occipital-temporal regions support the processing of the individual aspects that make up a study event (e.g. object information), while the hippocampal and parahippocampal regions are involved in reconstructing the associations between aspects of the study event. Consistent with this speculation, occipital-temporal activation is observed when subjects are required to retrieve information about object identity compared to object location [18,19].

The hippocampal regions that responded to associative recollection also responded with greater activation for new compared to old items during item recognition. One interpretation of these results is that both retrieval of associative information and the processing of novel information may activate the hippocampus. However, it is also possible that the old item condition was associated with a relative decrease in hippocampal activation due to the fact that the old items had been previously processed. In order to assess this possibility we directly compared the experimental conditions to the motor control condition. The hippocampal regions showed increased activation, relative to the control task, for both the associative and new conditions ($p < 0.05$, corrected for a 4 mm sphere region of interest centered on the hippocampal regions presented in Table 1), but showed no significant increase or decrease in the old-item condition relative to the control task. These results suggest that the associative and new conditions were preferentially engaging the hippocampal region.

Hippocampal activation related to the processing of novel information has been reported before [20–22], and has been interpreted as indicating that novel items engage hippocampal dependent encoding processes more so than familiar items. The finding that the hippocampal regions that are involved in recollection are also involved in the processing of novel items may explain why comparisons of well remembered items to new items that are not remembered sometimes does not lead to significant hippocampal activation [16]. Indeed, in the current study a direct comparison of the associative and new item conditions yielded no significant differences in hippocampal activation.

The blocked design used in the current study was useful in separating the processes involved in associative and item recognition, and in showing that the two types of recognition tests involved distinct temporal lobe regions. However, blocked designs are limited in the sense that they do not allow the separation of steady state processes

from event related processes [23]. For example, it is not clear whether the temporal lobe regions that were involved in associative compared to item recognition reflected the successful retrieval of different types of information, or whether they reflected differences in retrieval strategies in the two types of memory tests. Future studies that contrast steady state activation and activation related to specific events will be necessary to further tease apart the different processes that support associative and item recognition judgments.

CONCLUSION

The current results indicate that associative recognition and item recognition recruit partially distinct regions of the temporal lobe. Occipital-temporal lobe regions were involved in both types of recognition, however, hippocampal and parahippocampal regions were related to recollection of associative information but were not related to old item recognition.

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