Distinct roles for medial temporal lobe structures in memory for objects and their locations

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Long-term memory encoding and retrieval critically depend on a system of interconnected structures in the medial temporal lobe (MTL), including the hippocampus and the surrounding entorhinal, perirhinal, and parahippocampal cortices. Damage to these structures produces profound memory deficits; however, the unique contribution to memory of each of these structures remains unclear. Here we have used functional magnetic resonance imaging (fMRI) to determine whether the perirhinal and parahippocampal cortices show differential memory-related activity. Based on the distinct patterns of cortical input to these two areas, we reasoned that these structures might show differential activity for spatial and object recognition memory. In each of 11 subjects, we found that the perirhinal cortex was active during both spatial and object memory encoding, while the anterior parahippocampal cortex was active only during spatial encoding. These data support the idea that MTL structures make distinct contributions to recognition memory performance.

Results

Recognition memory performance

A description of the tasks is given in Figure 2. In alternating blocks of trials, subjects performed an object or spatial recognition memory task. Item recognition (percent correct) across all blocks of trials, subjects performed an object or spatial recognition memory task. Item recognition (percent correct) across all subjects during the functional scans did not differ for the two tasks (F1,10 < 1; P > 0.10). The average performance was 77% correctly recognized items for the object task and 76% for the spatial task. Performance as measured by d-prime also did not differ for the two tasks (F1,10 < 1; P > 0.10). The average d-prime rate was 2.22 for the Object task and 2.16 for the Spatial task. Subjects’ reaction time in the two tasks was also not significantly different.
suggesting that subjects used differential processes to solve the
differences were seen in ventral and dorsal stream visual regions,
difficulty. With whole-brain scanning, in a pilot subject, clear
across brain regions could not be attributed to differences in task
task. Accordingly, any task-dependent activation differences
was 1211 msec for the Object task and 1096 msec for the Spatial
activity in the perirhinal cortex.
locations (see Fig. 5), and there was no task-specific encoding
task was seen throughout the ventral visual stream. In contrast, a
during encoding that was stronger for the Object than the Spatial
mance of the Object and Spatial recognition memory tasks.
using anatomically defined regions of interest, we compared ac-
tivity in the perirhinal and parahippocampal cortices during per-
formance of the Object and Spatial recognition memory tasks. Figure 4 shows the location of significant task-specific fMRI ac-
tivity during encoding across the group of 11 subjects. Activity
during encoding that was stronger for the Object than the Spatial
task was seen throughout the ventral visual stream. In contrast, a
region in the anterior parahippocampal cortex bilaterally was selectivity active when subjects were encoding locations. The
perirhinal cortex was active during encoding of both objects and
locations (see Fig. 5), and there was no task-specific encoding
activity in the perirhinal cortex.

Figures 5 and 6 show the location of the activity seen in the
group analysis in the perirhinal and parahippocampal cortex for
each subject individually. Across the group and in each of the
individual subjects, there was significant activity in the perirhi-
nal cortex during encoding that was not different between the
two tasks (Fig. 5). Encoding activity in the perirhinal cortex was
located in both banks of the collateral sulcus, and there was bi-
lateral activation in seven subjects.
The anterior parahippocampal cortex was significantly more
active during the Spatial task than during the Object task, and
this differential activity was seen in each of the 11 subjects (Fig.
6). The activation in the anterior parahippocampal cortex was
located in both banks of the collateral sulcus, immediately pos-
terior to the perirhinal–parahippocampal border, and was pre-
dominately lateralized to the right hemisphere. However, seven
subjects showed this activation bilaterally. This spatial encoding
activation did not extend throughout the entire rostro-caudal
extent of the parahippocampal cortex, but was limited to the
most rostral portion of the parahippocampal cortex (~8–12 mm;
two to three functional coronal slices).

Figure 7 shows the averaged perirhinal, anterior parahippo-
campal, and posterior parahippocampal cortex activation for all
subjects during the encoding phase of both tasks. There was a
significant difference in activity during the two tasks only in the
anterior parahippocampal cortex (P < 0.001), where there was
greater activity during spatial encoding than during object en-
coding. There was a trend for the perirhinal cortex to be more
active during object encoding, but this was not significant
(P = 0.08).

We concentrated our analysis on the encoding phase of the
tasks because activity during the recognition phase could reflect
either recognition of the repeated stimuli or encoding of the
ovel stimuli. However, we found similar results across regions
during the recognition phase. The perirhinal cortex and the pos-
terior parahippocampal cortex were active during the recogni-
tion phase for both the Spatial and Object tasks (P < 0.01). Unlike
encoding, the anterior parahippocampal cortex was not active
during the recognition phase of either task (P > 0.10). None of
the regions showed significant activity above baseline during the
delay period (P > 0.10).

Discussion
The results from the present experiment suggest that compo-
nents of the MTL make distinct contributions to memory perfor-
ance. We found differences in activity in the perirhinal and
parahippocampal cortices for visual object and spatial recogni-
tion memory. A region in the anterior part of the parahippocampal
cortex was active only when subjects were encoding stimuli
in the Spatial memory task. In contrast, the perirhinal cortex was
similarly active when subjects performed the Object and the Spa-
tial memory tasks. The posterior parahippocampal cortex was
active during both object and spatial encoding.

It has been previously suggested that the perirhinal and
parahippocampal cortices may play distinct roles in visual object
and spatial memory, respectively (Suzuki and Amaral 1994a). The
data from the present experiment provide the first direct evi-
dence that such a functional distinction exists. One unexpected
finding of the present experiment was that the spatial activation
in the parahippocampal cortex was restricted to the anterior por-
tion. To our knowledge, there are no anatomical studies of the
MTL that have analyzed tracer injections restricted to this ante-
rior region that might suggest an anterior-posterior gradient in
the input of spatial information to the parahippocampal cortex.
The data from the present study raise this possibility, which would be an interesting topic for a future anatomical study.

Behavioral studies in monkeys and humans have reported spatial impairments resulting from lesions of the parahippocampal cortex (Jones and Mishkin 1972; Bohbot et al. 1998; Ploner et al. 2000; Malkova and Mishkin 2003). It is interesting to note, however, that in a recent study (Malkova and Mishkin 2003), one animal with a parahippocampal cortex lesion was unimpaired on a spatial memory task (object–place association), while the rest of the animals in this lesion group were impaired. Postmortem analysis of the lesion in the unimpaired animal revealed tissue sparing in the anterior parahippocampal cortex. Although this is just one animal, this finding is consistent with the present study and suggests that the anterior parahippocampal cortex might be critical for certain kinds of spatial memory.

In a recent study, Sommer et al. (2005) reported an area of activation in the right anterior medial temporal lobe that was correlated with memory for the location associated with an object. Using an event-related design, these authors correlated activity during encoding an object–location association with retrieval success when presented with either an object cue or a location cue. They found that activity in a small region in the right anterior MTL during encoding correlated exclusively with spatial encoding processes. That is, greater activity in this region during encoding predicted greater retrieval success with a location cue. The results in the present study support and extend this finding. Their anterior MTL activation overlaps exactly with the anterior parahippocampal cortex. Although this is somewhat surprising, given that the perirhinal cortex receives the majority of its cortical input from higher-order visual object association areas (see Fig. 1). However, the perirhinal cortex receives strong input from the parahippocampal cortex, which could be the source of spatial information to this area. The perirhinal cortex has been shown to be critical for both visual and tactile recognition memory performance (Buffalo et al. 1999). The present data suggest that the perirhinal cortex is similarly involved in spatial recognition memory.

An alternative possibility is that because spatial locations were repeated, the activity seen in the perirhinal cortex during spatial encoding actually reflected the retrieval of objects previously associated with a given location. Although this is important to consider, we believe that the previous interpretation better fits our data for several reasons. First, as shown in Figure 3, in a pilot subject, we found a clear dissociation in activity between ventral occipitotemporal and parietal areas for the Object and Location tasks.
In sum, the present findings add to a growing body of literature indicating that the structures of the medial temporal lobe make distinct contributions to memory. Moreover, the unique activations of the medial temporal lobe cortical regions we observed were consistent with differential anatomical input to this region. Future studies combining careful anatomical segregation of the medial temporal lobe with high-resolution scanning (e.g., Beauchamp et al. 2004) should provide further insight into the contribution of different medial temporal lobe structures to learning and remembering.

Materials and Methods

Subjects and experimental tasks

Eleven healthy subjects (seven male and four female) were recruited for functional imaging according to approved NIH protocols. All subjects gave informed consent.

During functional scanning, all subjects performed randomly interleaved blocks of the visual object and spatial recognition memory tasks (Fig. 2). For both tasks, the stimuli were trial-unique, relatively nonverbalizable, colorful patterns (Miyashita et al. 1991). These stimuli were chosen because amnesic patients with MTL damage are impaired at recognizing these stimuli with delays of 6 sec and longer, suggesting that these tasks rely on intact long-term memory systems (Buffalo et al. 1998). In the present study, the delays ranged from 18 to 33 sec. Using a button box, subjects performed an Old/New recognition judgment on either the stimulus (Object task) or the location of the stimulus on the screen (Spatial task).

Through several pilot behavioral experiments, the Object and Spatial recognition memory tasks were equated for difficulty.

In the encoding phase of both tasks, the subjects were presented a series of six stimuli in varying locations on a computer screen. There were 16 possible stimulus locations. Each stimulus was presented for 2500 msec with a 500-msec interstimulus interval (ISI). Immediately preceding this phase, subjects were instructed either to “Memorize the Object” (visual Object task) or to “Memorize the Location” (Spatial task). Then, during a delay period, a scrambled image of a test stimulus was presented six times at the center of the screen at the same rate as the test stimuli (2500 msec, 500 msec ISI). During this delay phase, subjects were instructed to “Watch the Picture.” The same scrambled image was used throughout the experiment. Finally, during the recognition phase, six stimuli were again presented at the same rate (2500 msec, 500 msec ISI). During the recognition phase of the visual Object task, three of the stimuli were repeated from the encoding phase, and three were new stimuli. Subjects were cued to “Recall the Object” and used a button box to make an Old/New recognition judgment. In the Object task, none of the six stimuli in the recognition phase was presented in a location that was used during the encoding phase of this block. During the recognition phase of the Spatial task, three of the stimuli were presented in the same location as a stimulus was presented during the encoding phase, and three were presented in new locations for this block. Subjects were cued to “Recall the Location” and used a button box to indicate recognition. All of the stimuli used in this phase were new...
Figure 7. Average task activity. Averaged across all 11 subjects, the perirhinal cortex was active during the encoding phase of both the Object task (blue bar) and the Spatial task (red bar). In contrast, the anterior parahippocampal cortex was significantly more active during spatial encoding (red bar). The posterior parahippocampal cortex was active during both object and spatial encoding.

Perirhinal and parahippocampal borders

To localize the areas in the MTL that were active during the two tasks, we created an anatomical atlas that included the perirhinal cortex and the parahippocampal cortex for each individual subject according to the method described by Insausti et al. (1998). The perirhinal and parahippocampal cortices consist of tissue in the collateral sulcus bilaterally. Because the collateral sulcus has a highly variable shape and length (Insausti et al. 1995), we felt most confident about the cortical localization of the activations on individual brains, in the absence of spatial interpolation resulting from stereotaxic normalization. The landmarks we used for the borders of the perirhinal and parahippocampal cortices were as follows: The perirhinal cortex consists of tissue in both banks of the collateral sulcus, bilaterally, beginning 2 mm rostral to the level of the limen insula, or tempo-frontal junction. Although in primates, the more anterior temporopolar cortex is considered part of the perirhinal cortex (Suzuki and Amaral 1994b), we did not include this cortex in our mask of the perirhinal cortex because we did not obtain sufficient signal in this region in most of our subjects. The caudal limit of the perirhinal cortex was identified as 4 mm posterior to the level of the gyrus intralimbicus, or the caudal end of the uncus. At this level, the parahippocampal cortex replaces the perirhinal cortex in the collateral sulcus, and it replaces the entorhinal cortex medially. The caudal border of the parahippocampal cortex has not been as extensively characterized as the perirhinal cortex; accordingly, we considered the parahippocampal cortex to extend through the caudal extent of the hippocampus.

Data analysis

AFNI (Cox 1996; Cox and Hyde 1997) was used for removing the first two images of each functional series, motion correction (Cox and Jesmanowicz 1999), and statistical analyses. Following motion correction, all eight runs were concatenated prior to being submitted to a two-factor [TASK (Object or Spatial) and PHASE (encode/delay/recognition)] multiple regression resulting in a total of six regressors. Averaged time series were created by selectively averaging the time points during each of the three PHASE levels for both tasks. These time series data were then converted to percent change using the post-recognition phase as baseline and shifted by three images (4.5 sec) to account for hemodynamic delay. The area under the averaged time series curve for each condition were submitted to a mixed effects three-factor ANOVA using subjects as a random factor and TASK and PHASE as fixed factors.

Individual analyses

Unbiased extraction of regionally specific averaged time series data were obtained using a combination of three masks applied to each individual’s thresholded data. The first mask was an anatomical atlas of pre-specified regions of interest created on the high-resolution anatomical images. This anatomical mask was created using the landmarks for the borders of each region described above. The next mask was a whole-brain mask that eliminated voxels with an MR intensity less than the median image MR intensity value (see AFNI-3dAutomask). This mask was used to reduce the probability of including noisy voxels by eliminating non-brain voxels and voxels with insufficient signal to noise to detect small percent signal changes. The third mask was derived from the group ANOVA analysis by thresholding the Full Model F statistic (F = 5.42; P < 0.00001) and the a priori comparison of means t-statistic (P < 0.05), that is, voxels that were significantly differentially active during the two tasks. The intersection of these three masks provided the data for the individual contrasts shown in Figures 5 and 6. For Figure 7, using the same masks, the average activity during encoding was calculated for each subject across each of the three regions.

Group analysis

For the group contrast data shown in Figures 4, 5, and 6, we combined the anatomically defined masks across subjects. We aligned the anatomical masks using AFNI’s Talairach alignment, added the masks from all 11 subjects, and then created a combined mask for each anatomical region that included all voxels that were present in at least nine of the 11 subjects. This procedure was used to exclude effects due to extreme anatomical variability.

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