

Separate Neural Bases of Two Fundamental Memory Processes in the Human Medial Temporal Lobe

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The participation of medial temporal-lobe structures in memory performance was examined by functional magnetic resonance imaging of local blood oxygenation level-dependent signals. Signals were measured during encoding into memory complex scenes or line drawings and during retrieval from memory of previously studied line drawings or words. Encoding tasks yielded increased signals for unfamiliar information in a posterior medial-temporal region that were focused in the parahippocampal cortex. Retrieval tasks yielded increased signals for successfully remembered information in an anterior medial-temporal region that were focused in the subiculum. These results indicate that separate components of the human medial temporal-lobe memory system are active during distinct memory processes.

In humans and other species, the medial temporal-lobe memory system is essential to declarative memory processes underlying remembrance for new events and facts (1). Injury to this system yields global amnesia, a profound and pervasive inability to remember new information, in humans, monkeys, and rats. The medial temporal-lobe memory system consists of multiple structures, differing in their neural cytoarchitecture and connectivity, that may be classified as belonging to two major regions. The hippocampal region is composed of the subiculum, the CA fields, and dentate gyrus. The parahippocampal region, which provides major inputs to the hippocampal region (2), is composed of parahippocampal and perirhinal cortices. Entorhinal cortex is variably classified as belonging to either region. In monkeys and rats, different components of the medial temporal-lobe memory system mediate separable memory processes (3). There is, however, no evidence at present about functional specialization within the human medial temporal-lobe memory system.

Activation in the medial temporal-lobe system was examined in six normal, right-handed subjects (five men, one woman, aged 24 to 27 years) with functional magnetic resonance imaging (fMRI) in which blood oxygenation level-dependent con-

trast was measured by a gradient echo spiral sequence (4, 5) (Fig. 1). Each subject performed two memory tasks: a retrieval task and an encoding task (6). Before fMRI scanning for the retrieval task, subjects were shown and asked to remember achromatic line drawings of common objects and animals (7). During scanning, subjects saw words in two conditions. In one condition, most of the words were the names of previously seen drawings. In the other condition, most of the words were the names of other drawings that had not been presented. Subjects judged whether each word was or was not the name of a previously seen drawing—a judgment requiring retrieval of memory for studied drawings. Subjects accurately retrieved memories for the drawings as evidenced by a mean of 88.5% correct memory judgments. For the encoding task (8), subjects saw, during scanning, color pictures of indoor and outdoor complex scenes. They were asked to judge whether each picture depicted an indoor or outdoor scene, and to remember the pictures for a later memory test. In one condition, pictures were seen for the first time. In another condition, pictures were shown repeatedly. Thus, the two conditions contrasted encoding novel versus familiar scenes into memory.

Statistical analyses (9) revealed three activations consistent across subjects: one in the retrieval task, and two in the encoding task. In the retrieval task, five of six subjects showed greater activation in an anterior medial temporal-lobe location during performance with words that were the names of studied drawings versus words that were the names of unseen drawings (Fig. 2). The anterior activation that occurred when memories for drawings were retrieved successfully was focused in the subiculum, a

component of the hippocampal region. In the encoding task, five of six subjects showed activation in a posterior medial temporal-lobe location that was greater when encoding novel pictures than when encoding familiar pictures. This activation was focused in parahippocampal cortex, a component of the parahippocampal region. Both activations were bilateral. In addition, five of six subjects showed right frontal-lobe activation for novel pictures in the inferior frontal sulcal region between middle and inferior gyri.

To further substantiate the dissociation between two medial temporal-lobe activations, the subiculum and the parahippocampal cortex were outlined bilaterally on anatomy images (10), and the percentages of significantly activated pixels in those regions of interest were analyzed statistically. The analysis revealed a double dissociation between memory activations, with greater activation in the subiculum for the retrieval than for the encoding task, but greater activation in the parahippocampal cortex for the encoding than for the retrieval task (Fig. 3).

The separate activations occurred while subjects performed two different tasks, encoding and retrieval, with two different sorts of materials, color scenes and words. To verify that the activations were related to the memory tasks rather than the materials, two additional subjects participated in a control study with a similar design except that only one kind of material, line draw-

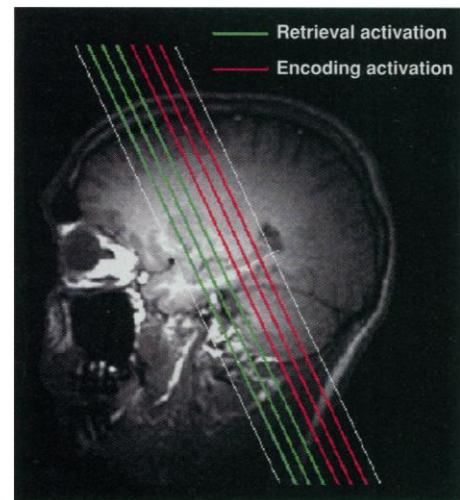


Fig. 1. Locations of MRI structural and functional images collected on a 1.5-T scanner (G.E. Signa). Parasagittal images were used to select eight 7-mm contiguous sections, shown as lines, that covered the hippocampus in a plane perpendicular to its long axis. Medial temporal-lobe activations associated with the retrieval task were found in anterior sections (shown in green) and activations associated with the encoding task were found in posterior sections (shown in red).

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ings, was seen during scanning for both memory tasks. Before scanning, subjects saw the names of drawings (6). For the retrieval task, subjects judged whether drawings corresponded to the previously studied words. There was greater activation in the subiculum during retrieval performance with drawings that did, versus those that did not, correspond to previously studied words. For the encoding task, subjects saw a different set of drawings, some appearing once only and others repeatedly, and judged whether each drawing depicted a living or nonliving object. There was greater activation in the parahippocampal cortex during encoding of unfamiliar than familiar drawings. These convergent findings indicate that the separate medial-temporal activations represent anatomical distinctions in memory processes associated with encoding and retrieval tasks.

The dissociable activations that occurred during retrieval and encoding tasks are consistent in general terms with other imaging studies of memory performance (8, 11), but the memory processes associated with those activations may not be best characterized as ones of retrieval and en-

coding per se. Hippocampal activation could reflect recollective memory processes guiding deliberate remembrance of a previous episode. Parahippocampal activation could reflect other memory processes that distinguish between familiar and unfamiliar stimuli. Such processes may be salient also for retrieval tasks where recognition can be guided on the basis of novelty, such as for familiar versus unfamiliar faces or objects. Memory researchers (12) have noted a fundamental distinction between processes mediating recollection and familiarity. This distinction may account for the common experience of recognizing something or somebody as familiar without recollecting the specific basis of that familiarity.

Current knowledge about the structural and functional organization of the medial temporal-lobe memory system derives almost exclusively from experiments with monkeys and rats. In broad terms, high-level unimodal and polymodal cortical regions provide convergent inputs to the parahippocampal region (13). The parahippocampal cortex receives especially strong projections from high-level visual areas (13). It is plausible, therefore, that parahip-

pocampal cortex mediates memory processes that discriminate novel from familiar visual stimuli. Indeed, there is some evidence in monkeys that the parahippocampal region, particularly perirhinal cortex, is especially important for visual recognition memory tasks that can be performed on the basis of novelty discrimination (3, 14). The functional correspondence between specific medial temporal-lobe regions in monkey and human brains is, however, unknown. Human memory is influenced by many cognitive abilities, such as language, that are not evident in monkeys or rats.

The parahippocampal region, in turn, provides nearly two-thirds of the neocortical inputs to the hippocampal region, including the subiculum (13). The subiculum transmits outgoing information from the hippocampal region to other brain regions. The CA1 region of the hippocampus projects primarily to the subiculum. In humans, damage to the CA1 region appears sufficient to produce clinically significant amnesia (15). Also, the subiculum is affected early and severely in Alzheimer's disease, in which a declarative memory disorder is often the first and most severe behavioral symptom (16). The subiculum also provides the major subcortical output of the hippocampal region via the fornix. In humans, fornix damage can yield global amnesia (17). Further, there is evidence in monkeys (3) and rats (18) that the fornix may play an especially important role in memory tasks that demand the flexible expression of memories rather than familiarity discrimination. It is plausible, therefore, that subiculum activation provides an index of the hippocampal mediation of flexible mnemonic processes that are critical for many declarative memory tasks.

A vast experimental and clinical literature substantiates the vital role of the medial temporal-lobe memory system in the remembrance of events and facts. Characterizing the specific memory processes mediated by different components of the medial temporal-lobe memory system is a use-

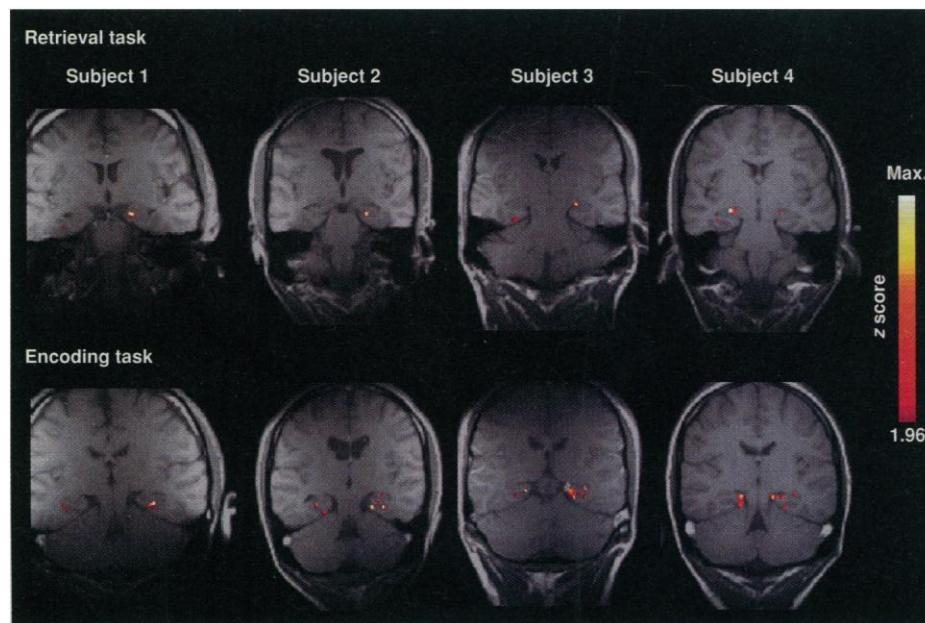


Fig. 2. Medial temporal-lobe regions significantly activated in the retrieval and encoding memory tasks in individual subjects; each column depicts two oblique sections from one subject. Colored pixels exceeded the statistical threshold (9) and were overlaid on corresponding anatomy images. Functional maps were normalized and linearly scaled in each section such that the lowest significant z scores (1.96) appear in dark red and the highest in bright yellow or white. The left side of each picture shows the left side of the brain. The top row shows activations in the subiculum during the retrieval memory task that were greater for words corresponding to previously seen than unseen line drawings (Subjects 1, 2, and 3) or greater for line drawings corresponding to previously seen than unseen words (Subject 4). Sections, from left to right, correspond to the second, third, fourth, and fourth locations in Fig. 1. The bottom row shows activations in the parahippocampal cortex during the encoding memory task that were greater for novel than for repeated color scenes (Subjects 1, 2, and 3) or greater for novel than for repeated line drawings (Subject 4). Sections for Subjects 1, 2, and 3 correspond to the fifth location in Fig. 1, and the section for Subject 4 corresponds to the sixth. Although activations depicted here are predominantly right-sided, there was no overall asymmetry across all sections and subjects.

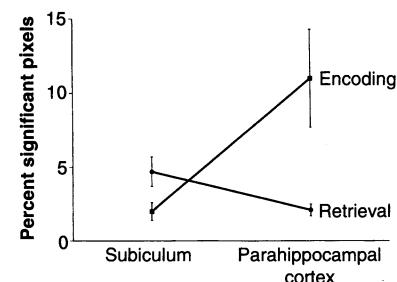


Fig. 3. Percentages of significantly activated pixels during retrieval and encoding tasks in subiculum and parahippocampal cortex. Brackets show standard error of the mean.

ful step toward discovering how this system serves so many aspects of learning. Such specific characterization has been limited largely to ablation studies in monkeys and rats. The present findings indicate that functional neuroimaging can provide insights about specialization of mnemonic processes in the human medial temporal-lobe memory system. Such specializations are likely both to parallel, owing to shared evolutionary histories, and to differ from, owing to what is uniquely human, those found in monkeys and rats.

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- Informed consent was obtained from all participants. Structural images were longitudinal relaxation time (T1)-weighted, flow-compensated spin-warp repetition time (TR) = 500 ms, minimum echo time (TE). Eight functional images were collected every 2880 ms through use of a gradient echo spiral sequence sensitive to apparent transverse relaxation time (T2*) with four interleaves (TR = 720 ms, TE = 40 ms, flip angle = 65°). There were 984 (or 1808 in the control study) and 1296 (or 1520) functional images collected per subject for the retrieval and encoding tasks, respectively. Two 5-inch-diameter local receive coils were used with five subjects, and a whole head coil was used for the sixth subject and both subjects in the control study. Head movement was minimized through use of a "bite-bar" formed with each subject's dental impression; motion artifact was examined automatically for all scans.
- Subjects viewed 80 line drawings presented twice 24 hours and once 30 min before scanning. During the 342-s retrieval scan, subjects saw eight sets of 20 words each presented individually for 1500 ms with 500-ms intervals between words. Alternate New and Old sets comprised, respectively, 18 new words (names of nonstudied drawings) and 2 old words (names of studied drawings) or 18 old words and 2 new words. Subjects were instructed visually to squeeze a pneumatic bulb for names of studied pictures in Old sets or for names of nonstudied pictures in New sets. During the 467-s encoding task, subjects saw 12 sets of eight pictures, with each set including four indoor and four outdoor scenes presented individually for 3000 ms with 1800-ms intervals between pictures. Alternate sets comprised New pictures not seen before and two Old pictures presented repeatedly. Subjects were instructed visually to squeeze for indoor scenes and to remember the pictures. The order of stimulus presentation (Old/New or New/Old) was counterbalanced across subjects for both tasks. The control study was identical in organization except that subjects studied 102 words three times each just before scanning; saw in the retrieval task (648 s) 12 sets of 17 line drawings each presented for 2000 ms with 1000-ms intervals in alternate blocks of 15 new and 2 old or 15 old and 2 new drawings; and responded to drawings of living objects in the encoding task (547 s) during which they saw 28 sets of four living and four nonliving objects each presented for 2000 ms with 500-ms intervals.
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- Activation maps were determined by analyzing the correlation for each pixel between signal intensity and a reference function computed by convolving a square wave at the task frequency (alternating conditions in each task) with a data-derived estimate of the hemodynamic response function [K. J. Friston, P. Jezzard, R. Turner, *Hum. Brain Mapping* **1**, 153 (1994)]. Pixels were selected that (i) exceeded the statistical criterion of $z > 1.96$ (representing significance at $P < 0.025$, one-tailed) and (ii) were not eliminated with a 2 by 2 pixel median filter that eliminated isolated selected pixels.
- For all subjects, the subiculum was outlined anatomically in three anterior sections and the parahippocampal cortex in three posterior sections without functional data overlays. Regions were defined by landmarks [D. G. Amaral and R. Insausti, in *The Human Nervous System*, G. Paxinos, Ed. (Academic Press, San Diego, CA, 1990), pp. 711-755; H. M. Duvernoy, *The Human Hippocampus* (Verlag, Munich, 1988)]. Percentages of significantly activated pixels were analyzed in a repeated-measures analysis of variance with factors of brain region (subiculum/parahippocampal cortex), hemisphere (left/right), and memory task (retrieval/encoding). The only significant effect was a region \times task interaction, $F(1, 5) = 11.97$, $P = 0.018$, reflecting more activation in the subiculum during the retrieval than during the encoding task [$t(5) = 3.94$, $P = 0.01$], but more activation in the parahippocampal cortex during the encoding than during the retrieval task [$t(5) = 2.77$, $P < 0.05$]. There were also trends for more activation during the encoding than the retrieval task, and more activation in the parahippocampal cortex than in the subiculum (P values = 0.11).
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Trafficking of Matrix Collagens Through Bone-Resorbing Osteoclasts

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An intracellular pathway for proteins liberated from mineralized matrix during resorption was identified in osteoclasts. Analysis by confocal microscopy of sites of active bone resorption showed that released matrix proteins, including degraded type I collagen, were endocytosed along the ruffled border within the resorption compartment and transcytosed through the osteoclast to the basolateral membrane. Intracellular trafficking of degraded collagen, as typified by the resorbing osteoclast, may provide the cell with a regulatory mechanism for the control of tissue degradation.

Osteoclasts are multinucleate bone cells with the capacity to degrade the extracellular matrix of the skeleton by the process of bone resorption, thus participating in the homeostasis of bone and calcium (1). Osteoclasts resorb mineralized tissues after a series of cellular polarization events (2). Cytoskeletal rearrangement creates an F-actin-rich structure, the tight seal, that encloses a specialized secretory membrane, the ruffled border. Protons and proteases cross

the ruffled border and degrade bone matrix through demineralization and proteolytic activity, with calcium and type I collagen fragments being liberated into a resorption compartment beneath the cell. These products reach the extracellular space, where their levels correlate with bone resorption activity (3).

It has been assumed that degraded bone matrix leaves the resorption site by leakage from under the osteoclast during cell migration or is released en masse at the termination of the resorption cycle when the resorption compartment is disassembled. Alternatively, an enclosed resorption site could be maintained if there were intracel-

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