

Remembering episodes: a selective role for the hippocampus during retrieval

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Some memories are linked to a specific time and place, allowing one to re-experience the original event, whereas others are accompanied only by a feeling of familiarity. To uncover the distinct neural bases for these two types of memory, we measured brain activity during memory retrieval using event-related functional magnetic resonance imaging. We show that activity in the hippocampus increased only when retrieval was accompanied by conscious recollection of the learning episode. Hippocampal activity did not increase for items recognized based on familiarity or for unrecognized items. These results indicate that the hippocampus selectively supports the retrieval of episodic memories.

Studies of neuropsychological patients have revealed that damage to the medial temporal lobe can produce a deficit in declarative memory, the conscious memory for facts and events¹. Due to the diffuse nature of many medial temporal lobe lesions (which may include entorhinal, perirhinal and parahippocampal cortices as well as hippocampus), it is difficult to ascertain the role of individual structures. Although some evidence indicates that the hippocampus is particularly important for declarative memory²⁻⁵, other evidence suggests that the hippocampus only supports memories embedded in a particular spatial and temporal context⁶⁻¹⁰, a form of declarative memory known as episodic memory. Thus, controversy currently surrounds whether hippocampal patients exhibit a selective deficit only in their memory for episodes or a more general impairment in conscious memory.

Despite the great wealth of information provided by studies of neuropsychological patients, these investigations may ultimately be unable to resolve the complete role of the hippocampus in memory because they cannot fully distinguish encoding and retrieval deficits. The re-experience of time and place during retrieval differentiates episodic memories from other forms of declarative memory. As a result, it is critical to study how the hippocampus is involved in retrieval processes to understand whether the hippocampus is uniquely involved in episodic memory. Unfortunately, hippocampal patients tend to suffer from a pronounced learning deficit that may obscure the true nature of an additional retrieval deficit^{3,9}.

Neuroimaging techniques provide a means for measuring patterns of neural activity associated with retrieval processes in normal subjects. This allows for retrieval processes to be isolated from those processes associated with learning. Functional neuroimaging has identified medial temporal lobe regions that are important for establishing memories¹¹⁻¹⁵. For instance, activity in parahippocampal cortex during encoding predicts whether memories will later be judged as episodic, based on familiarity,

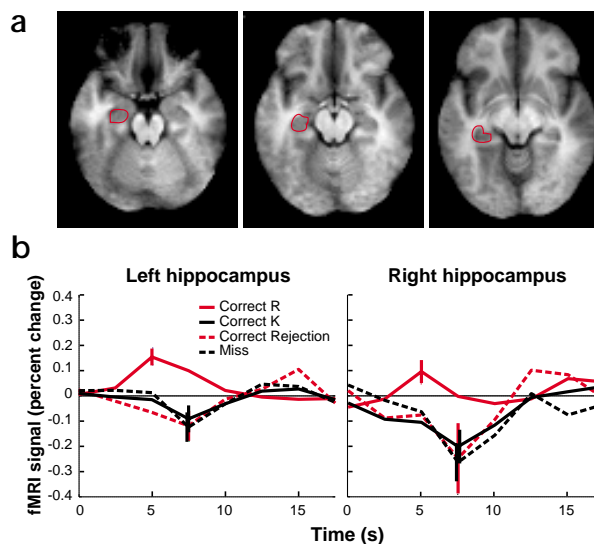
or forgotten¹⁶. Although neural activity has also been measured during memory retrieval, activity in the hippocampus has rarely been reported¹⁷.

To determine the role of the hippocampus in memory retrieval, we used functional magnetic resonance imaging (fMRI) to measure changes in blood flow associated with neural activity in normal subjects during episodic and non-episodic retrieval. Subjects were told to memorize each word for a subsequent memory test. They were not given any instructions on memorization techniques nor was there a secondary task. Twenty minutes later, as functional images were acquired, we presented the subjects with studied and unstudied items. We asked them first to determine whether they had studied the word, and then to classify their memory for the word as episodic or non-episodic. Thus, on each trial the subject made two button-press responses. If the hippocampus is selectively involved in episodic memory, then it should be particularly active during the retrieval of memories that subjects classify as episodes.

To categorize the type of memory retrieved on each trial, subjects performed the remember-know task¹⁸ during scanning, in which subjects classify their memories as either episodic (remember) or based on familiarity (know). This task has been used extensively to identify episodic recollections under a variety of conditions. Accuracy for remember and know judgments can be dissociated by several manipulations, including dividing attention at study or altering the frequency of studied words^{19,20}. As the first step of the task, subjects indicated whether they confidently recognized the item. For recognized items, subjects then made a remember (R) response if they could recollect the moment the item was studied or a know (K) response if they had no such recollection. R responses could, for example, be based on perceptual details subjects noticed or associations they made with the word during study. Know (K) responses indicated that the word was highly familiar but unaccompanied by recollec-

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Fig. 1. Results from anatomically defined hippocampal regions of interest. **(a)** Sections from the anatomical template with the left hippocampal region of interest outlined in red. The right hippocampus was selected using the same anatomical landmarks in the right hemisphere. **(b)** Averaged event-related responses in the hippocampus from 11 subjects. In left hippocampus, correct R response amplitudes were reliably larger than zero ($t_{10} = 4.56$, $p < 0.001$), indicating a significant increase from baseline. The correct R response amplitudes were also larger than the correct K ($t_{10} = 4.62$, $p < 0.001$), correct rejection ($t_{10} = 3.76$, $p < 0.01$), and miss response amplitudes ($t_{10} = 4.29$, $p < 0.01$). In right hippocampus, correct R response amplitudes were reliably larger than correct K ($t_{10} = 3.10$, $p < 0.05$) and miss response amplitudes ($t_{10} = 4.47$, $p < 0.01$). Error bars represent \pm one standard error (between subjects) of estimated response amplitudes.



tions of the specific moment the word was presented. Encoding conditions were the same for all studied words. However, at retrieval, episodic content was only available for items given an R response. The fMRI data were selectively averaged according to these different types of retrieval events.

RESULTS

Typically, subjects are more accurate at discriminating between studied and unstudied items using R responses than K responses^{19,20}. When subjects incorrectly recognize an unstudied item, they are more likely to classify the memory as a K response than as an R response because details of the study episode should be absent. Our behavioral results showed this expected pattern: the R false alarm rate was 1%, and the K false alarm rate was 33%. In addition, subjects accurately identified old items when they made an R response (mean hit rate, 42%; $d' = 2.58$). Subjects also accurately identified old items using the K response (mean hit rate, 73% under the assumption that all remembered items were also known; $d' = 1.17$). Despite some difference in the number of trials in each condition (correct R, mean \pm s.d., 45.0 ± 16.6 ; correct K, 32.9 ± 7.4 ; correct rejection, 17.7 ± 5.5 ; miss, 26.0 ± 11.0), each of the included conditions contained sufficient numbers of trials (at least 10 per subject) for analysis.

Analysis of the fMRI data indicated that the hippocampus was active selectively during episodic retrieval. We identified a hippocampal region of interest in each hemisphere, which consisted of the CA fields and dentate gyrus, using only anatomical landmarks. These regions of interest (ROIs) were determined blind to activation patterns in each subject. Event-related responses averaged within these regions of interest are shown in Fig. 1. In the left hippocampus, correct R trials produced significant increases in MR signal relative to the fixation baseline. MR signal associated with correct R responses was also significantly greater than signal associated with correct K responses, correct rejection of new items, and miss responses, in which subjects did not recognize old items. In individual subject analyses, correct R responses resulted in greater MR signal than correct K responses in 10 of the 11 subjects.

Importantly, correct K, correct rejection and miss responses were of equal size, and all differed reliably from correct R responses. Although functional MRI data cannot determine the absolute level of activity of a structure, our data suggest that the hippocampus was not more active when items were familiar than when they were unfamiliar. Only episodic retrieval produced a pattern of hippocampal activity that was distinguishable from activity produced by unrecognized items.

Table 1. Locations of differential R and K activity.

Region	H	Talairach coordinates			t-value
		x	y	z	
R > K					
Middle frontal gyrus	L	-30	32	45	5.89
Posterior cingulate gyrus	R	13	-23	45	4.28
Precentral gyrus	R	51	-9	40	4.17
Inferior parietal gyrus	L	-43	-56	40	5.60
Inferior parietal/angular gyrus	R	53	-58	35	3.64
Inferior frontal gyrus	R	55	7	25	6.61
Inferior parietal gyrus	L	-50	-41	25	5.23
Middle temporal gyrus	L	-44	-63	20	5.84
Posterior cingulate gyrus	R	17	-57	15	4.47
Superior temporal gyrus	L	-58	-39	10	8.32
Caudate nucleus	L	-12	16	5	4.28
Insula	L	-36	-8	0	5.76
Hippocampus	L	-32	-23	-10	5.26
Parahippocampal gyrus*	R	21	-38	-10	4.52
Fusiform gyrus	R	34	-55	-15	6.06
K > R					
Anterior cingulate gyrus*	R	11	16	40	5.14
Anterior cingulate gyrus	L	-12	14	40	3.97
Superior frontal sulcus*	R	23	52	25	5.60

Approximate anatomical locations, hemispheres (H), and coordinates in standard stereotaxic space³³ are given for regions showing significant differential activity between correct R and correct K responses ($t_{10} > 3.17$, $p < 0.01$ uncorrected). *Regions that also showed a significant difference between correct K and correct rejection responses.

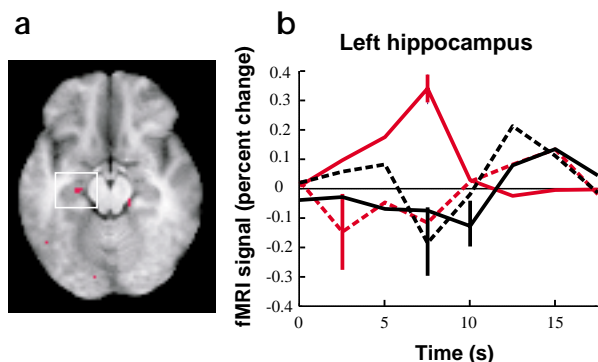


Fig. 2. Results from hippocampal region of interest using a statistical map. **(a)** Statistical map comparing correct R and correct K response amplitudes. Red voxels represent larger amplitudes for correct R responses. Only voxels with a t -value greater than a threshold of 4.95 are shown. No voxels in this slice showed greater response amplitudes for correct K than for correct R trials. The white square highlights a differentially active region in the left hippocampus (Talairach coordinates, $-32, -23, -10$). **(b)** Event-related responses for differentially active voxels within the left hippocampal region. The response amplitude for correct R trials was greater than for correct K trials ($t_{10} = 8.82$, used for pixel selection), correct rejection trials, miss trials, and zero.

The pattern of activity in the right hippocampus was similar. Correct R responses were larger than correct K and miss responses, but the difference between correct R and correct rejection responses did not reach statistical significance. The larger effect in left hippocampus may be due to the verbal nature of the stimuli. Studies of memory encoding have also found material-specific lateralization in the medial temporal lobe^{11,12}.

A second analysis identified regions throughout the brain that showed reliable differences between correct R and correct K response amplitudes (Table 1). This analysis localized the differential hippocampal activity to a region within central portions of the left hippocampus (Fig. 2). In addition, greater activation associated with correct R responses than with correct K responses was evident bilaterally in regions of the inferior parietal gyrus and in the left middle frontal gyrus. Several regions also showed greater activity for correct K responses than for correct R responses, including left anterior insula, right superior frontal sulcus and bilateral anterior cingulate. The regions outside the hippocampus overlap with areas commonly activated in memory retrieval tasks^{21,22}.

A difference in hippocampal activation may exist between correct K and correct rejection responses that was too small to be detected by our study. However, the overall pattern of activity suggests that the absence of a difference between correct K and correct rejection responses in hippocampus was not due to a general lack of sensitivity. In several of the brain regions listed in Table 1, correct K responses were larger than correct rejection responses, indicating that the analyses could detect such differences. The pattern of hippocampal activity cannot simply be explained by the amount of time spent on the task. The two decisions leading to a correct R response (1.7 s) were made faster than those for a correct K (2.2 s; $t_{10} = 12.41$, $p < 0.01$), correct rejection (2.3 s; $t_{10} = 6.56$, $p < 0.01$), or miss response (2.4 s; $t_{10} = 7.86$, $p < 0.01$). Thus, subjects completed the trials that produced the greatest hippocampal responses in the least amount of time, suggesting that hippocampal activity is not the result of general mental effort.

DISCUSSION

The present results may explain why some previous studies have failed to find activation in the hippocampus during retrieval^{23,24}. Studies that average hippocampal activity across episodic and non-episodic retrieval are likely to find little activation. Our data predict this outcome because during episodic retrieval MR signal increased in the hippocampus, whereas during non-episodic retrieval it decreased; the same cancellation of signal may also have occurred in the K condition of another study that used the R-K procedure²⁵. It is likely that the K condition in this study²⁵ contained both episodic and non-episodic memories, because it used a version of the R-K task that may not adequately distinguish between episodic and non-episodic forms of memory. The way in which the subject is instructed to perform the R-K task has a profound effect on the classification of memories. If subjects decide in a single step whether an item is an R, a K or new, they will tend to use the R and K labels to indicate strong and weak memory²⁶, rather than episodic and non-episodic memory. The procedure used in the present study, in which subjects first decide if they recognize an item and subsequently decide for recognized items whether the item corresponds to an R or a K, seems to encourage subjects to apply the R and K labels as episodic and non-episodic memory.

Our results are consistent with theories asserting that the hippocampus is necessary for the retrieval of episodes, but provide no evidence that it is necessary for recognition based on familiarity. The present data do not directly address whether the hippocampus is important for the retrieval of other forms of non-episodic memory, such as memory for facts. Nevertheless, our results suggest that the hippocampus is not important for the retrieval of all forms of declarative memory. In addition, the role of this structure in retrieval must be time-limited, because memories acquired long before hippocampal damage can be retrieved normally³. A process of consolidation occurs over time so that eventually the hippocampus is no longer required even for episodic retrieval.

Selective lesions of the hippocampus in animals produce recognition deficits in some tasks²⁷, but leave performance unimpaired in other tasks²⁸. These results parallel the present findings, which suggest that the hippocampus is required only for some forms of recognition. Episodic memory cannot be directly assessed in animals. However, one critical feature of episodic memory is the retrieval of spatio-temporal context, which can be assessed in non-humans using contextual learning protocols. In contextual learning, animals must encode and retrieve the configuration of features that compose the context in order to perform the task. Hippocampal lesions cause specific impairments in these tasks²⁹. Lesions restricted to the hippocampus in rats, for example, produce deficits in contextual fear conditioning, though not in conditioning to discrete cues³⁰.

Episodic memories are the conjunction of features that compose a particular event. The function of the hippocampus during retrieval may be to help reinstate these complex conjunctions of features. The fMRI data presented here may provide a glimpse of the hippocampus as it binds together the disparate elements of a retrieved experience.

METHODS

Subjects. Twelve healthy, right-handed subjects were run in the experiment (age range 22–38). One subject was excluded from all analyses because of excessive motion during scanning. These studies were performed under a protocol approved by the UCLA Office for the Protection of Research Subjects.

Stimuli. Stimuli consisted of 108 target words and 27 lures. Each of the 9 functional scans contained 12 target words and 3 lures in a random order. A design with a relatively low number of lures was chosen to ensure that sufficient numbers of correct K trials were obtained, while maintaining reasonably high levels of accuracy. In each five-second trial, subjects were first prompted to decide whether or not they recognized the item (3 s), and subsequently for recognized items whether they remembered or knew it (2 s). Responses were recorded via button presses. If the item was not recognized, the subject pressed either button at the second prompt. Between trials, subjects maintained fixation for 15 s. Subjects were instructed to disengage from retrieval performance during the fixation period.

fMRI methods. A 3T GE Signa scanner with ANMR echo-planar upgrade was used for all functional imaging. A T2*-weighted gradient echo sequence was used to measure blood-oxygen level dependent contrast (TR, 2.5 s; TE, 45 ms) in 16 horizontal slices (voxel size, 3.125 × 3.125 × 5 mm). Each scan contained 15 trials.

AIR software³⁰ was used for image realignment, transformation into standard stereotaxic space, and spatial smoothing (6 mm Gaussian kernel) of data used in the group average. We divided each fMRI time series into 20-s blocks corresponding to each trial. We classified the subject's responses as either 'hit' or 'false alarm' for R, K and not recognized trials. We averaged the corresponding 20 s of fMRI data for each response type separately. There were too few R and K false alarms to allow further analysis of those trials. Over half of the subjects had less than 10 R and K false alarms combined. All subsequent analyses considered only correct R, correct K, correct rejection and miss (incorrect not recognized) responses.

Response amplitudes were computed for the average event-related responses by fitting a gamma function to the data³². The gamma fitting procedure estimated both a lag and amplitude parameter for each averaged response of each subject.

For all analyses, response amplitudes were compared using a paired *t*-test, implementing a random-effects model. For the hippocampal analysis, response amplitudes were computed for anatomically defined regions of interest (CA fields and dentate gyrus) in each subject. The regions of interest were specified using the group anatomical template and verified in each subject's individual anatomy images. For the full brain analysis, paired *t*-tests were conducted at each voxel. Statistical parametric maps were then displayed for each contrast. The regional differences that are reported consist of at least five contiguous voxels that surpass a threshold of $p < 0.01$ ($t > 3.17$) without correction for multiple comparisons. These regions were localized on the normalized anatomical template and labeled using the nomenclature of Talairach and Tournoux³³.

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