Different nonlinear functions in hippocampus and perirhinal cortex relating functional MRI activity to memory strength

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Findings from functional MRI (fMRI) studies of recognition memory and the medial temporal lobe often suggest qualitative differences in the contribution of the hippocampus and perirhinal cortex. This interpretation is complicated by the fact that most of the methods intended to demonstrate qualitative differences also separate strong memories from weak memories. Thus, apparent qualitative differences might reflect quantitative differences in how measured activity in medial temporal lobe structures varies with memory strength. We tested the hypothesis that the relationship between activity at the time of study and subsequent memory strength is nonlinear in hippocampus and perirhinal cortex and also distinctly different in those two structures. We found that activity in the hippocampus was characterized by a positively accelerated function and that activity in the perirhinal cortex was associated with a statistically different, negatively accelerated function. Our results do not count against the possibility that these structures differ qualitatively in their contributions to memory. Rather, our findings show how an alternative interpretation based on quantitative differences can also account for a good deal of data, and they suggest that a demonstration of qualitative differences requires more stringent criteria than are achieved in most fMRI studies.

Declarative memory is the capacity to consciously remember facts and events and depends on the integrity of medial temporal lobe structures: the hippocampus, dentate gyrus, and subicular complex, together with the adjacent perirhinal, entorhinal, and parahippocampal cortices (1). One of the most widely studied examples of declarative memory is recognition memory—the ability to judge an item as having been encountered previously. Recognition memory is widely viewed as consisting of two qualitatively different components, recollection and familiarity (2, 3). Recollection involves remembering specific contextual details about a previous learning episode, whereas familiarity involves remembering that an item was presented but in the absence of contextual information about the learning episode itself.

Recollection and familiarity have been proposed to have a neuroanatomical basis within the medial temporal lobe (4). Specifically, it was proposed that recollection depends on the hippocampus and familiarity on the adjacent perirhinal cortex. This qualitative distinction between the functions of hippocampus and perirhinal cortex has stimulated a considerable amount of experimental work, particularly using functional MRI (fMRI) (for reviews, see refs. 5–7). However, the study of recollection and familiarity is complicated by the fact that the methods that have been used to separate recollection and familiarity also typically separate strong memories from weak memories, respectively (7, 8). This is problematic because recollection can be weak and familiarity can be strong (9). Accordingly, it is possible that an fMRI finding of increased hippocampal activity reflects strong memories (memory judgments made with high confidence, high accuracy, and fast reaction times), regardless of whether these memories reflect strong recollection, strong familiarity, or a combination of the two. Furthermore, weak memories may not result in increased activity in the hippocampus, regardless of whether such memories reflect weak recollection, weak familiarity, or a weak combination of the two. For example, accurate associative recognition (thought to depend on recollection) was associated with hippocampal activity when face–name pairs were remembered with high confidence but not when they were remembered with low confidence (10).

In the case of perirhinal cortex, the fMRI signal may exhibit a steep increase when memories are weak but a more shallow increase when memories are stronger. Such a finding need not mean that the perirhinal cortex is uninvolved in recollection. For example, the fMRI signal in perirhinal cortex for both single-item memory (11) and associative memory (12) was sensitive to variations in memory strength at the low end of the scale (activity associated with trials early in learning and with trials given confidence ratings of 1–5). In the same studies, the fMRI signal in perirhinal cortex was relatively insensitive to variations in memory strength at the high end of the scale (activity associated with trials late in learning and with trials given confidence ratings of 5 and 6).

An implication of these findings is that the typical relationship between memory strength and activity in the hippocampus and perirhinal cortex may be nonlinear (Fig. 1). The relationship between neural activity and the fMRI signal has sometimes been found to be linear, particularly in studies of sensory systems (13). Yet, little is known about this issue in the medial temporal lobe. Furthermore, there is no a priori reason to expect activity in the medial temporal lobe to scale linearly with a cognitive construct like memory strength (or even to exhibit the same characteristics in different medial temporal lobe structures). Thus, in the hippocampus, the relationship may be such that there is little detectable change of fMRI activity for weak memories but there is a steep increase in fMRI activity in the high range of the memory strength scale. Because recollection-based responses are typically associated with strong memories, this nonlinear pattern could explain the typical finding in hippocampus. That is, hippocampal activity is typically associated with strong memories (successful source memory and remember judgments), but not with weaker memories (unsuccessful source memory and know judgments) (14–16).

In perirhinal cortex, the relationship may be such that there is a steep increase of fMRI activity in the low range of the memory strength scale and little additional increase in activity for stronger memories. Because familiarity-based responses are typically associated with weak memories, a nonlinear pattern in perirhinal cortex could explain the typical finding in perirhinal cortex. Specifically, perirhinal activity has been detected when decisions were based on weak memories (e.g., unsuccessful source memory

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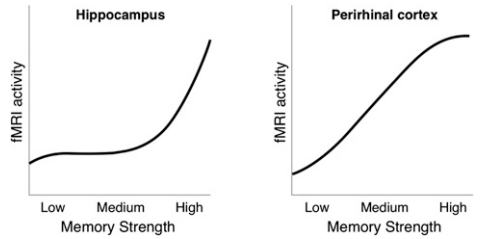

Fig. 1. Proposed nonlinear relationships between fMRI activity at encoding and subsequent memory strength (adapted from ref. 7).

or items with low confidence vs. forgotten items), but activity was no greater when decisions were based on stronger memories (e.g., successful source memory) (11, 14, 15).

Our study was not designed to confirm or reject the idea that recollection and familiarity are differentially supported by the hippocampus and perirhinal cortex, respectively. Instead, it was designed to investigate whether the shape of the functions relating activity in hippocampus and perirhinal cortex to memory strength might differ in a specific way. Such a finding would provide an alternative view of the fMRI activity that has often been reported in studies of these structures.

Participants were scanned while they studied a list of words and were then given a test of recognition memory outside the scanner for targets and foils using a 1–20 confidence rating scale (Fig. 2). Trials for studied words were sorted according to the level of confidence given on the recognition test. We then explicitly tested for nonlinear patterns of fMRI activity that related activity at study to subsequent memory strength.

Results

Behavioral Performance. The overall proportion of correctly recognized words was 82.9 ± 1.4% (hit rate 86.4 ± 1.7%; false alarm rate 20.6 ± 1.8%; $d' = 2.01 \pm 0.12$). The proportion of responses for targets (studied words) and foils (new words) at each level of confidence is presented in Fig. 3. Accuracy was highest for items given high confidence ratings (95.0 ± 2.2% correct, ratings from 17 to 20), lower for items given medium confidence ratings (73.0 ± 4.2% correct, ratings from 14 to 16), and lowest for items given low confidence ratings (46.5 ± 0.9% correct, ratings from 11 to 13). Confidence ratings are a well-established method for determining memory strength (17, 18). Accordingly, these three ranges of confidence ratings (high, medium, and low) thus reflect three levels of memory strength, and these three levels of memory strength were used in analysis of the fMRI data. [Note that our analysis was based on 3 levels of memory strength (not, for example, 5 or 10) because 3 was the largest number of bins we could construct and still have at least 10 trials in each bin for each participant].

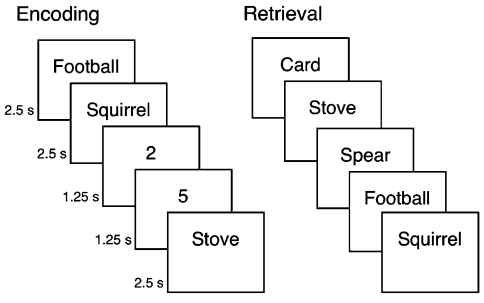

Fig. 2. Experimental design. During scanning, participants rated each of 360 words (2.5 s per word) as pleasant or unpleasant. The words were intermixed with baseline trials in which participants indicated whether a digit was odd or even (1.25 s per digit). At a surprise postscan test (about 15 min later), participants made old–new recognition judgments (1 = "definitely new"; 20 = "definitely old") for the 360 target words and 360 foil words.

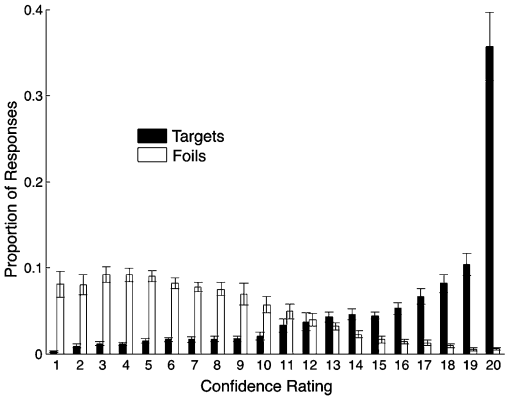

Fig. 3. Proportion of responses for targets (black bars) and foils (white bars) at each confidence level during the postscan recognition memory test (n = 17). Error bars indicate SEM.

fMRI Analyses. Using two different methods, we tested the suggestion that the function relating fMRI activity during study to subsequent memory strength is nonlinear in hippocampus and perirhinal cortex and also distinctly different in these two structures (Fig. 1). We analyzed brain activity at encoding as it related to subsequent low, medium, and high memory strength. The first method used voxelwise t tests to look for distinct patterns of fMRI activity that conformed to what is illustrated in Fig. 1. To test for one pattern (Fig. 1, *Left*), we looked for regions that discriminated between high and medium memory strength but did not discriminate between medium and low memory strength (*Materials and Methods*). A cluster was identified in left hippocampus (Table 1 and Fig. 4, *Left* column). In addition, we identified a cluster in left temporopolar cortex and another cluster in left parahippocampal cortex, but no cluster in perirhinal cortex. Whole-brain analysis identified regions outside the medial temporal lobe as well (Table 1).

To test for a different pattern (Fig. 1, *Right*), we looked for regions that discriminated between medium and low memory strength but did not discriminate between medium and high memory strength (*Materials and Methods*). A cluster was identified in right perirhinal cortex (Table 2 and Fig. 4, *Right* column).

Table 1. Regions exhibiting a positively accelerated relationship between brain activity at study and subsequent memory strength

		Talairach coordinates				Cluster size
		X	*Y*	*Z*	*T* value	(μL)
Regions in the medial temporal lobe						
L	Parahippocampal cortex	−25	−27	−12	3.4	376
L	Hippocampus	−17	−17	−16	5.0	976
L	Temporopolar cortex	−35	17	−20	3.9	768
Regions in the whole brain						
R	Cerebellum	39	−67	−20	5.0	7,112
R	Precentral gyrus	35	−25	54	3.3	1,668
R	Superior temporal gyrus	47	15	−16	3.8	1,560
L	Inferior frontal gyrus	−49	23	−4	11.0	18,784
L	Superior frontal gyrus	−5	41	44	13.2	23,104

Talairach coordinates indicate the location of the voxel with peak *T* value; L, left; R, right.

Table 2. Regions exhibiting a negatively accelerated relationship between brain activity at study and subsequent memory strength

		Talairach coordinates				Cluster size
		X	*Y*	*Z*	*T* value	(μL)
Regions in the medial temporal lobe						
R	Perirhinal cortex	37	−19	−24	3.0	456
Regions in the whole brain						
R	Middle temporal gyrus	51	−11	−18	7.2	5,360
L	Middle temporal gyrus	−55	−11	−14	5.9	2,368

See Table 1 for abbreviations.

In this case, at a voxelwise threshold of $P < 0.05$, the cluster was too small to be considered reliable (33 voxels rather than the minimum of 47 voxels). However, when the voxelwise threshold was adjusted to $P < 0.06$ (now requiring a minimum cluster size of 53 rather than 47 voxels), this cluster contained 56 voxels and reached a cluster-corrected threshold of $P < 0.05$. Whole-brain analysis identified regions outside the medial temporal lobe as well (Table 2). The findings from these *t* test analyses were identical in the medial temporal lobe when more lenient statistical thresholds for identifying clusters were applied (up to $P = 0.25$, corrected). That is, no other clusters were identified.

Fig. 4*B* shows the hemodynamic response functions for the three levels of memory strength in each identified region. The overall magnitude of each hemodynamic response function was computed by summing the β coefficients across all time lags (Fig. 4*C*).

The second method analyzed the data in a different way by directly testing for a specific pattern that related fMRI activity at study to the three levels of memory strength of remembered items (low, medium, and high). Accordingly, we carried out two regression analyses that complement the *t* test analyses described above. One regression analysis was designed to detect a specific positively accelerated function that was especially sensitive to the strongest memories and less sensitive to weaker memories (*Materials and Methods*). This analysis identified only one cluster in the medial temporal lobe where activity during study was positively accelerated in relation to subsequent memory strength. The cluster was located in left hippocampus (−23, −17, −10; 424 μL; Fig. 5, *Left* column). Note that this cluster is smaller than, but in a similar location as, the cluster in left hippocampus depicted in Fig. 4, *Left* column, and Table 1.

Another regression analysis was designed to detect a specific negatively accelerated function that was sensitive to weaker memories (*Materials and Methods*). This analysis identified two clusters in the medial temporal lobe. One cluster was located in left perirhinal cortex (−27, 13, −24; 472 μL) and the other in right perirhinal cortex (33, −11, −22; 528 μL) (Fig. 5, *Center* and *Right* columns). Note that the right perirhinal cluster is in nearly the same location and is approximately the same size as the right perirhinal cluster depicted in Fig. 4, *Right* column, and Table 2. The left perirhinal cluster was not detected by the first method (Fig. 4 and Table 2). The findings of the two regression analyses were the same in the medial temporal lobe when more lenient statistical thresholds for identifying clusters were applied (up to $P = 0.25$, corrected). That is, no other clusters were identified.

The hemodynamic response functions for the three levels of memory strength in each identified region, as well as the overall magnitude of each hemodynamic response function in each identified region, are shown in Fig. 5 *B* and *C*, respectively.

It is worth mentioning that we did carry out a (third) neutral analysis (one-way ANOVA for the low, medium, and high conditions). We found clusters in the same regions as we found in the regression analyses (i.e., left hippocampus, left perirhinal cortex, and right perirhinal cortex), and activity in these clusters in relation to memory strength was similar to the patterns illustrated in Fig. 5*C*. However, the left-sided clusters were too small to be considered reliable (left hippocampus, 32 voxels; left perirhinal, 20 voxels; minimum needed = 47).

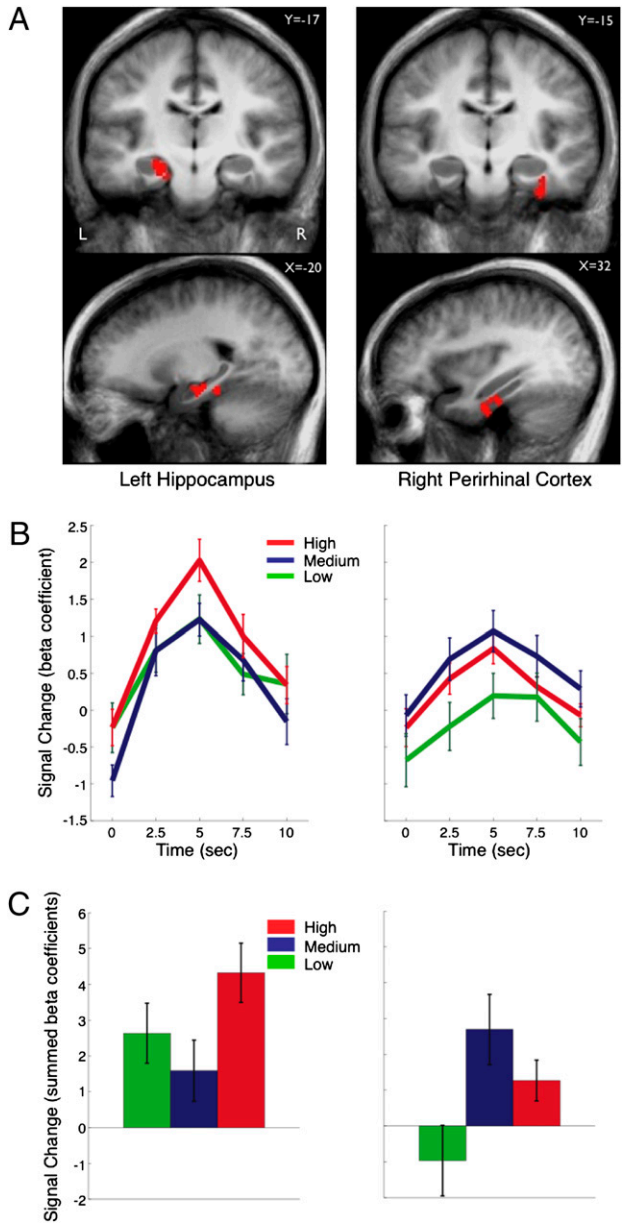

Fig. 4. The results of voxelwise, paired *t* tests ($n = 17$) between the three levels of memory strength (low, medium, and high). Activity in left hippocampus was identified by using two voxelwise *t* tests to identify regions where activity differed between high and medium memory strength but did not differ between medium and low memory strength (*A*, *Left* column). Activity in right perirhinal cortex was identified by using two voxelwise *t* tests to identify regions where activity differed between medium and low memory strength but did not differ between medium and high memory strength (*A*, *Right* column). For each identified region, hemodynamic response functions are depicted (relative to baseline) for the three levels of memory strength (*B*). (*C*) Overall activity in each region for the three levels of memory strength. Error bars indicate SEM. *X*, left/right Talairach coordinate; *Y*, anterior/posterior Talairach coordinate; L, left; R, right.

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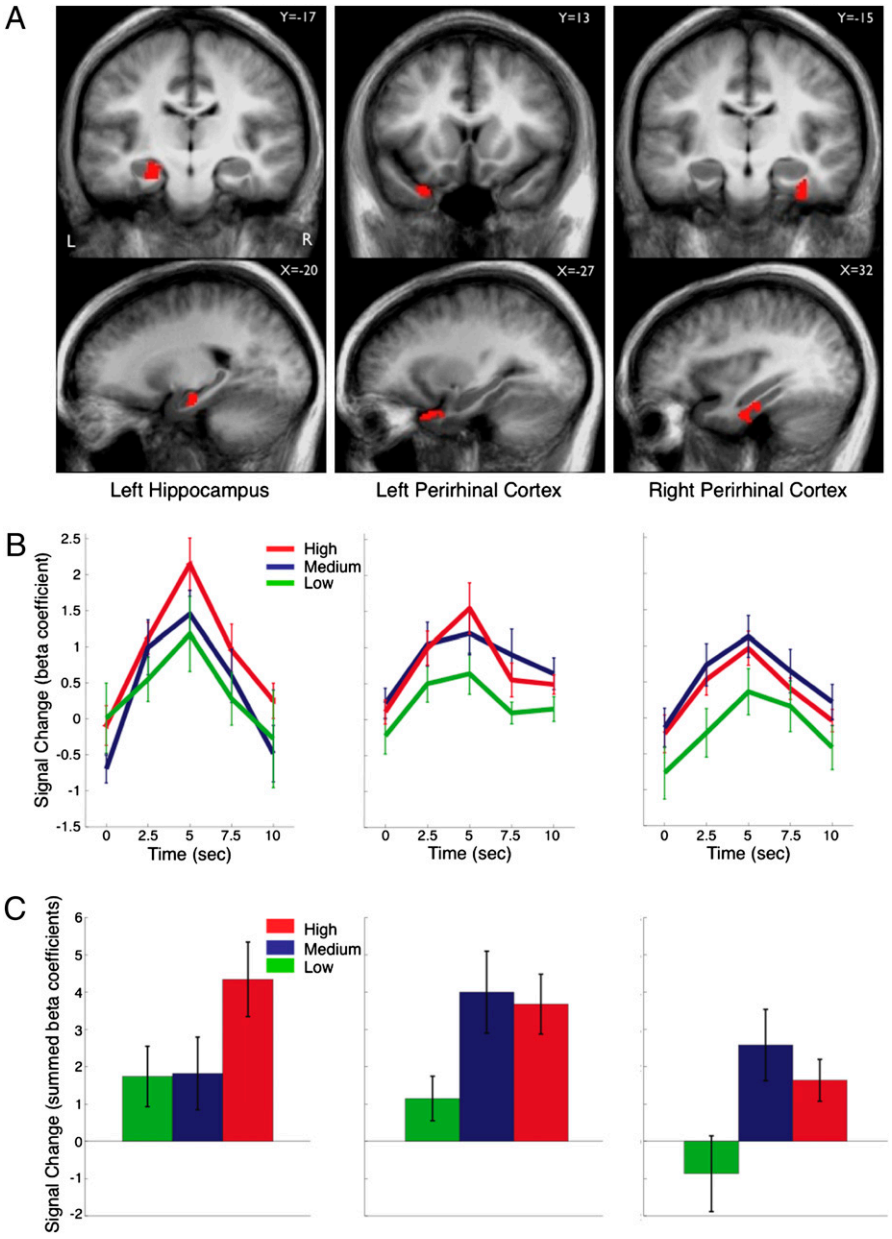

Fig. 5. The results of regression analyses (n = 17) that tested for specific nonlinear response functions relating brain activity at encoding to subsequent memory strength (low, medium, and high). A positively accelerated response function was especially sensitive to strong memories and was characteristic of activity detected in the left hippocampus (*A*, *Left* column). A different, negatively accelerated response function was sensitive to weaker memories and was characteristic of activity detected bilaterally in perirhinal cortex (*A*, *Center* and *Right* columns). For each identified region, hemodynamic response functions are depicted (relative to baseline) for the three levels of memory strength (*B*). (*C*) Overall activity in each region for the three levels of memory strength. Error bars indicate SEM. *X*, left/right Talairach coordinate; *Y*, anterior/posterior Talairach coordinate; L, left; R, right.

In summary, our analyses indicate that activity in the left hippocampus was especially sensitive to strong memories, and activity in the perirhinal cortex was especially sensitive to differences between weaker memories. With respect to the findings in the hippocampus, note that hippocampal activity was greatest in association with high memory strength, but activity was also detected when memory strength was low. Specifically, activity associated with the low memory-strength condition was greater than baseline activity (Figs. 4*C* and 5*C*; $P < 0.05$). The ability to detect memory-related activity in hippocampus is likely related to the selection of a suitable baseline condition (19). In any case, the finding of hippocampal activity above baseline in the low memory-strength condition counts against the idea that hippocampal activity is associated only with the strongest (recollection-based) memories.

Discussion

We examined the relationship between brain activity during study and subsequent memory strength for what was learned. We tested the hypothesis that the relationship between fMRI activity during study and subsequent memory strength is nonlinear in hippocampus and perirhinal cortex and also distinctly different in these two structures.

An analysis of high vs. medium and medium vs. low memory strength revealed a different pattern of activity for hippocampus and perirhinal cortex. Specifically, a cluster in left hippocampus discriminated between high and medium memory strength but did not discriminate between medium and low memory strength (Fig. 4, *Left* column). A cluster in left temporopolar cortex and a cluster in left parahippocampal cortex exhibited the same pattern. In contrast, a cluster in right perirhinal cortex discriminated between medium and low memory strength but did not discriminate between medium and high memory strength (Fig. 4, *Right* column). These results indicate that the relationship between the blood oxygen level-dependent (BOLD) signal and subsequent memory strength was nonlinear within the hippocampus and perirhinal cortex.

The findings were similar when we used regression to directly test for a pattern that was especially sensitive to strong memories or for a pattern that was especially sensitive to differences between weaker memories. Specifically, a similar cluster in left hippocampus exhibited activity that was especially sensitive to strong memories (Fig. 5, *Left* column), whereas a similar cluster in right perirhinal cortex exhibited activity that was especially sensitive to differences between weaker memories (Fig. 5, *Right* column).

The finding of different relationships between fMRI activity during encoding in hippocampus and perirhinal cortex and subsequent recognition memory strength bears on the proposal that these structures may have different roles in the two components of recognition: recollection and familiarity. As discussed elsewhere (7), the methods used to separate recollection from familiarity also separate strong memories from weak memories. Accordingly, the proposal that recollection depends on the hippocampus and familiarity depends on perirhinal cortex might be recast in terms of the memory strength that typically underlies each type of judgment. Specifically, the nonlinear functions identified in this study could mean that hippocampal activity might be associated more with the formation of strong memories, regardless of whether they reflect strong recollection, strong familiarity, or a combination of the two. Similarly, perirhinal activity might reflect the formation of weaker memories, regardless of whether they reflect weak recollection, weak familiarity, or a weak combination of the two. Note, however, that our findings do not count against interpretations of hippocampal and perirhinal function that emphasize qualitative differences in their contributions. These findings simply identify an alternative to the specific proposal that recollection and familiarity are fundamental to understanding the functions of the hippocampus and perirhinal cortex.

Findings similar to ours have been observed in other fMRI studies. In one study (10), participants were scanned while learning novel face–name associations and were then given a memory test immediately after scanning. Activity in the hippocampus during learning was higher for associations that were subsequently identified correctly compared with incorrectly identified associations. Because associative recognition is thought to be based on recollection, this finding is consistent with the idea that the hippocampus subserves recollection. However, this hippocampal activity was detected only when participants had high confidence in their judgments (78% correct) and not when they had lower confidence in their judgments but still performed above chance (58% correct). This finding accords with our results in suggesting that the fMRI signal in hippocampus is relatively insensitive to weak memories, including weak recollection. Note that in our study, activity in the hippocampus was in fact detected when memory strength was low, but activity was much greater when memory strength was high (Figs. 4*C* and 5*C*).

In another study (11), activity at encoding was correlated with subsequent memory using a 6-point confidence scale. Specifically, clusters were identified by correlating activity with confidence ratings of 1 through 5. The only region identified in the medial temporal lobe was in "rhinal cortex" (perirhinal and entorhinal cortex). For confidence ratings of 6, activity in this cluster was no higher than it was for confidence ratings of 5. This result is consistent with our findings of a nonlinear relationship between fMRI activity at encoding and subsequent memory strength in perirhinal cortex (Fig. 4, *Right* column and Fig. 5, *Center* and *Right* columns).

Lastly, in an associative learning task (12), activity in perirhinal cortex as well as in the hippocampus increased as task performance improved. A nonlinear relationship between BOLD signal and memory strength was observed in the perirhinal cortex. Specifically, perirhinal activity increased rapidly early in learning and then leveled off as learning continued. This finding also accords with our results, as it suggests that the fMRI signal in perirhinal cortex is sensitive to variations in memory strength at the low end of the scale and relatively insensitive to variations in memory strength at the high end of the scale. This observation appears to hold true even for recollection-based tasks, such as the associative learning task used by Law et al. (12).

The present study demonstrates that the relationship between the BOLD signal during study and subsequent memory strength is nonlinear in the hippocampus and perirhinal cortex, and that the shape of the two nonlinear functions is different in the two structures. One must exercise caution in attaching functional significance to these different nonlinear functions, specifically the notion that the different shapes across brain structures imply qualitative differences in the memory processes they subserve (13). To attach functional significance to these nonlinear functions would require a better understanding of the relationship between neural activity and the BOLD signal in each structure. In addition, our results indicate that the strength of a memory has a large influence on activity in medial temporal lobe structures. Accordingly, when comparing activity in a medial temporal lobe structure across conditions of interest, it is important to equate for memory strength. For additional discussion of the challenges involved in demonstrating a qualitative difference in brain activity between different structures, see ref. 20.

Materials and Methods

Participants. Seventeen right-handed volunteers (10 female; mean age, 26.1 y; range, 20–39 y) recruited from the University of California, San Diego community gave written informed consent before participation.

Materials. The stimuli were 720 nouns with a mean frequency of 27 (range, 1–198) and concreteness ratings greater than 500 (mean, 573) (21). Half the words were assigned to three 120-word study lists, and half the words served as foils for the retrieval test. The assignment of words to the study and test conditions was counterbalanced across participants.

Procedure. Participants were scanned in three separate runs of 120 words each, during which the 360 target words were presented (Fig. 2). Participants made a pleasant/unpleasant rating for each word (2.5-s presentation time) and were not informed that their memory for words would be tested. Responses were collected via an MR-compatible button box (Current Designs). An odd/even digit task was intermixed with word presentation and served as a baseline against which the hemodynamic response was estimated (18). For the digit task, participants saw a digit (1–8) for 1.25 s and indicated by button press whether the digit was odd or even. Digit task trials (140 trials per scan run) were pseudorandomly intermixed with the encoding trials with the following constraints: each scan run began and ended with at least 12 digit trials, and the number of digit trials placed between the words was 0, 2, 4, or 6 so as to fit within the 2.5-s repetition time (TR; see below). The mean interval between words was 1.5 s (range, 0–7.5 s). Following scanning (15-min delay), participants took a surprise postscan recognition memory test. They saw all 360 words from the scan session (targets) and 360 novel foils one at a time in random order. For each word, participants made a recognition confidence judgment on a scale from 1 to 20 (1 = "definitely new" and 20 = "definitely old"). There was no time limit for responses. Before testing, participants completed a short practice block to ensure that they understood the instructions and the confidence rating scale.

fMRI Imaging. Imaging was carried out on a 3T GE scanner at the Center for Functional MRI (University of California, San Diego). Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (TR, 2,500 ms; echo time (TE), 30 ms; flip angle, 90°; matrix size, 64×64; field of view, 22 cm). The first five TRs acquired were discarded to allow for T1 equilibration. Forty oblique coronal slices (slice thickness = 5 mm, 0 gap) were acquired perpendicular to the long axis of the hippocampus and covering the whole brain. Following the three functional runs, a high-resolution structural image was acquired using a T1-weighted, fast spoiled gradient-echo (FSPGR) pulse sequence (flip angle, 8°; TE, 3.0 ms; 172 slices; 1 mm slice thickness; matrix size, 256×256; field of view, 25 cm).

fMRI Data Analysis. fMRI data were analyzed using the AFNI suite of programs (22). Functional data were corrected for field inhomogeneity with field mapping data collected before functional scanning, coregistered in three dimensions with the whole-brain anatomical data, slice-time corrected, and

coregistered through time to reduce effects of head motion. Large motion events, defined as TRs in which there was >0.3° of rotation or >0.6 mm of translation in any direction were excluded from the deconvolution analysis by censoring the excluded time points but without affecting the temporal structure of the data. We also excluded the TRs immediately preceding and following the motion-contaminated TRs. Trials in which there was no response for the pleasantness rating task (mean = 4.5 per participant) or in which there was no response or a wrong response for the odd/even judgment task (mean = 46.4 per participant) were excluded from further analysis. Confidence ratings from the recognition memory test were used to assign the targets to four conditions: misses (ratings from 1 to 10), hits with low confidence (ratings from 11 to 13), hits with medium confidence (ratings from 14 to 16), and hits with high confidence (ratings from 17 to 20). There were 49.1 ± 6.2 trials, 40.5 ± 7.5 trials, 51.2 ± 5.5 trials, and 219.1 ± 12.9 trials in these conditions, respectively.

The behavioral vectors and six vectors that coded for motion (three for translation and three for rotation) were used in deconvolution analyses of the fMRI time series data. The baseline trials were not modeled. The deconvolution method does not assume a shape of the hemodynamic response, and the fit of the data to the model was estimated for each time point independently. The resultant fit coefficients (β coefficients) represent activity vs. baseline in each voxel for a given time point and for each of the four trial types (misses and hits with three levels of confidence). This activity was summed over the expected hemodynamic response (0–12.5 s after trial onset) and taken as the estimate of the response for each trial type (relative to the digit task baseline). The activity associated with misses was modeled in the response functions but was not used for further analysis. Note that activity associated with subsequently forgotten items (misses) can be substantial and is thought to represent task-irrelevant mental activity at the time of study that leads to the encoding of information other than the presented words (23).

Initial spatial normalization was accomplished using each participant's structural MRI scan to transform the data to the atlas of Talairach and Tournoux (24). Statistical maps were also transformed to Talairach space, resampled to 2 mm^3, and smoothed using a Gaussian filter (4 mm full width at half maximum, FWHM). We also carried out a separate alignment procedure centered on the medial temporal lobe (MTL) (for details, see *SI Materials and Methods*).

Following individual deconvolution analysis, parameter estimate maps from each participant were entered into group-level analyses. The first group-level analysis was designed to look for regions where brain activity differentiated strong memories from weaker memories but where activity did not differentiate among weaker memories (Fig. 1, *Left*). Accordingly, we used two voxelwise *t* tests to look for regions where activity was different for high and medium memory-strength conditions (voxelwise threshold, $P < 0.05$) but was not different for medium and low memory-strength conditions (voxelwise threshold, $P > 0.05$). Thus, we looked for voxels where the first contrast was significant and the second one was not (i.e., we exclusively masked the results of the first *t* test with the results of the second). The resulting statistical map was cluster corrected for multiple comparisons (see below).

The second group-level analysis was designed to look for regions where brain activity differentiated weak memories from stronger memories, but where activity did not differentiate among stronger memories (Fig. 1, *Right*). Here, we used two voxelwise *t* tests to look for regions where activity was different for low and medium memory-strength conditions (voxelwise threshold, $P < 0.05$) but was not different for medium and high memory-strength conditions (voxelwise threshold, $P > 0.05$). Thus, just as in the first analysis (above), we exclusively masked the results of the first *t* test with the results of the second. The resulting statistical map was cluster corrected for multiple comparisons (see below).

The third and fourth group-level analyses were designed to complement the first and second analyses, respectively. The third analysis used regression to test for the presence of a particular predicted pattern across the three memory-strength conditions. Specifically, we created one regressor to detect a positively accelerated function that was especially sensitive to the strongest memories and less sensitive to weaker memories. For the low, medium, and high memory-strength conditions the regressor weights were [−1 −1 2]. The fourth group-level analysis used regression to test for the presence of a specific negatively accelerated function that was sensitive to weaker memories and less sensitive to stronger memories. For the low, medium, and high memory-strength conditions the regressor weights were [−2 1 1].

Note that these regression analyses tested for the same patterns of activity as did the *t* tests and would therefore be expected to yield similar results. We present the regression analyses because they analyze the data in a different way.

Statistical maps were thresholded at a voxelwise *P* value of <0.05. For the MTL analyses, group statistic maps were masked using the MTL template from the ROI-Demons alignment procedure (see *SI*) to include only regions of the MTL. A cluster correction technique was used to correct for multiple comparisons, and Monte Carlo simulations were used to determine how large a cluster of 2-mm^3 voxels was needed to be statistically meaningful ($P < 0.05$) (25, 26) within the volume of the MTL (minimum cluster extent of 47 contiguous voxels). For whole-brain analyses, the minimum cluster extent was 195 voxels.

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