Medial temporal lobe activity can distinguish between old and new stimuli independently of overt behavioral choice

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We collected fMRI data and confidence ratings as participants performed a recognition memory task that intermixed recently studied words and new (non-studied) words. We first replicated a typical finding from such studies; namely, increasing activity in medial temporal lobe structures with increasing confidence in the old/new decision. Because there are greater proportions of old items at higher confidence levels, such activity could be related to the confidence ratings or to whether items are old or new. When activity associated with old and new items was analyzed separately, we found that activity in the hippocampus bilaterally, as well as in anterior parahippocampal gyrus, was associated with the actual old/new status of the items rather than to which items participants believed to be old. Accordingly, activity in the medial temporal lobe can be modulated by the old/new status of stimuli and does not always track the behavioral response.

fMRI | hippocampus | parahippocampal gyrus | recognition memory

The medial temporal lobe (MTL) supports declarative memory (1). However, it remains unclear how the structures within the MTL (including the hippocampus and adjacent cortical structures) participate in declarative memory processes. For example, it has been proposed that the response of the MTL during recognition memory tasks may be modulated by the strength of declarative memory, as measured by the confidence with which memory decisions are made (2–9). For example, in one study activity during learning in both hippocampus and adjacent perirhinal cortex was positively related to the subsequent strength of recognition memory (7). A similar proposal is that the MTL responds to retrieval success rather than retrieval effort (10). Alternatively, it has been proposed that MTL responds to whether a stimulus is old or new (11), sometimes independently of a participant's behavioral response (12). Several studies of recognition memory have examined fMRI activity during retrieval of recently acquired material (2–5). In these studies, the data have been analyzed in two ways. One approach has been to focus on the relationship between fMRI activity and the confidence level associated with the recognition decision. Thus, in several studies, activity in the MTL has been associated with the items recognized with high confidence (a possible recognition signal) (4, 13, 14). In addition, activity in the perirhinal cortex was associated with items that were identified as new with the highest confidence (a possible novelty signal) (2, 4, 5).

A second approach has been to focus on the old/new status of the items, regardless of the confidence associated with the recognition decision. For example, based on the same data as in (4), it was found that activity in hippocampus and parahippocampal cortex was greater in association with old items than new items, regardless of how participants responded (12).

Recognition accuracy and recognition confidence are typically correlated, meaning that there is a greater proportion of old stimuli (targets) associated with high-confidence hits and a greater proportion of new stimuli (foils) associated with high-confidence correct rejections. Given this circumstance, one would expect these two approaches to yield similar findings. At the same time, it will not always be clear which factor is most important, the old/new status of the items or the confidence level of the recognition decision. The difficulty is that it will be unclear if a finding is related to the confidence level reported for the recognition memory decision or to the frequency with which old items appear. Prior studies that have obtained confidence judgments for recognition memory decisions (3, 4, 12) have not considered these two factors separately.

We scanned participants as they performed a recognition memory test for words using a 6-point confidence scale (Fig. 1*A*). We performed two kinds of analyses. First, we contrasted activity at different levels of confidence, regardless of the old/new status of the words (to compare our results to earlier studies that used this approach). Second, we examined the influence of confidence ratings on fMRI activity, but we considered the old items and the new items separately.

Results

Behavioral Performance. Fig. 1*B* depicts the distribution of old/new responses in the recognition memory test. The overall percentage correct score (68.4 ± 3.0%) was well above chance (t[12] = 6.08, $P < 0.001$). Overall d' was 1.07 ± 0.18. As expected, response accuracy was related to the confidence rating given for "old" responses (for "4", "5", and "6", accuracy was 45.0 ± 3.8%, 68.4 ± 4.6%, and 91.6 ± 2.1%, respectively) as well as to the confidence rating given for "New" responses (for "3", "2", and "1", accuracy was 74.2 ± 3.0%, 84.8 ± 3.0%, and 90.6 ± 1.7%, respectively). Reaction time (RT) data are presented in Table 1 for the six recognition memory confidence levels for both targets and foils.

fMRI Analyses. To begin, we analyzed the data to ask if our results conformed to what has been reported previously in similar studies. A frequently reported finding is that activity is greater in the hippocampus for the highest confidence trials (e.g., "6") than for lower confidence trials (e.g., "1"–"5") (3–5). Our analysis looked for regions where activity remained constant at a low level for recognition confidence levels 1 through 5 and increased for confidence level 6. This analysis revealed two regions of MTL including left hippocampus [x = −1, y = 19, z = −8; F (1, 12) = 7.22, $P < 0.05$; volume = 4,680 mm^3] and right hippocampus [x = 17, y = 37, z = −6; F (1, 12) = 6.77, $P < 0.05$; 5,016 mm^3]. We also conducted a linear trend analysis of the MTL data for recognition confidence levels 1–6. This analysis

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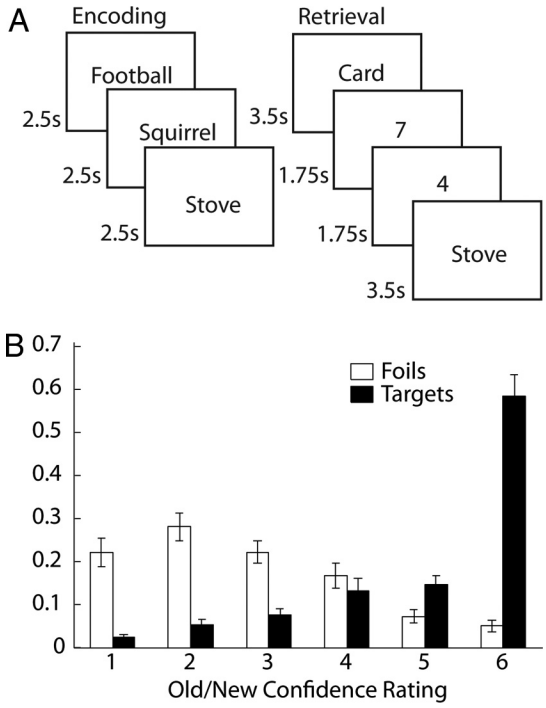

Fig. 1. Task design and behavioral performance. (*A*) Participants studied 360 words approximately 15 min before scanning. In the scanner, participants saw 360 targets and 360 foils and performed an old/new recognition memory task using a 6-point scale (1 = sure new, 6 = sure old). The words were separated by 2, 4, or 6 baseline trials where participants made odd/even judgments. (*B*) Participants distributed their responses across all 6 levels of old/new recognition confidence for both targets and foils.

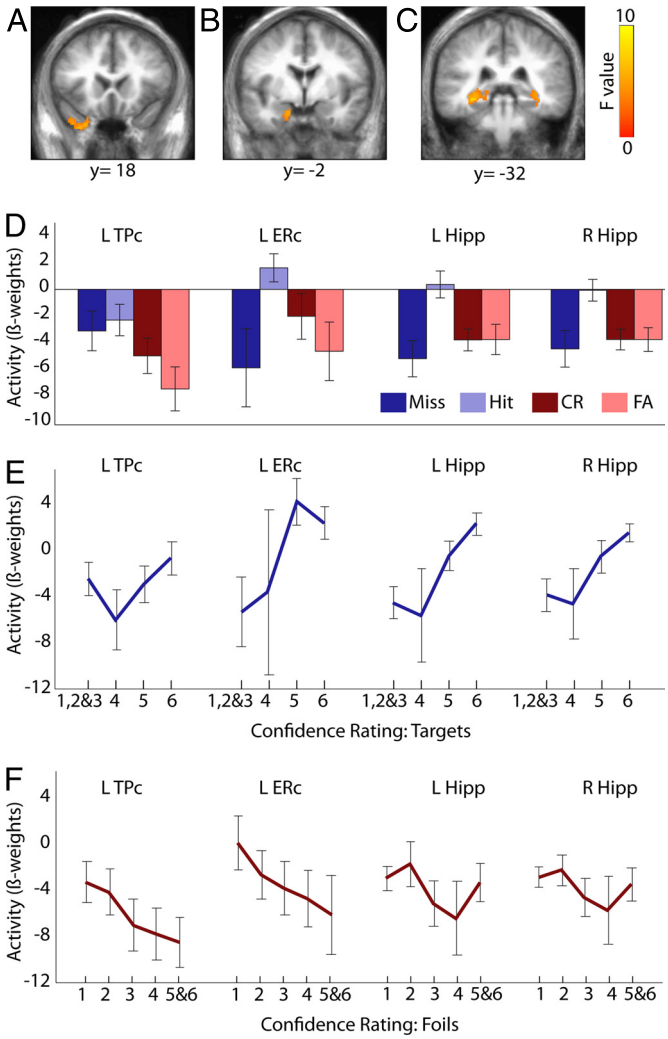

Fig. 2. fMRI analysis. An ANOVA revealed four regions in the medial temporal lobe where there were significant differences in activation for hits, misses, correct rejections, and false alarms: (*A*) left temporopolar cortex, (*B*) left entorhinal cortex, and (*C*) left and right hippocampus. (*D*) Mean activity in each of the four regions identified in the ANOVA. (*E*) In left and right hippocampus as well as in the left entorhinal cortex, activity increased in a linear fashion as confidence increased in the old/new judgment made to targets. (*F*) In the left temporopolar and left entorhinal cortices, activity decreased in a linear fashion as confidence increased in the old/new judgment made to foils. Some levels of confidence were combined because of low numbers of observations.

revealed a region in right temporopolar cortex [x = 17, y = −7, z = −16; F (1, 12) = 9.53, $P < 0.01$; 352 mm^3] where activity increased with increasing recognition confidence. Additional regions that emerged in the whole brain data for these two analyses appear in Table S1.

These first two analyses contrasted activity at different recognition confidence levels regardless of the old/new (target/foil) status of the stimulus. This approach could create difficulties for interpretation as mentioned previously, because the relative distribution of target and foil trials typically changes systematically with changes in recognition confidence (Fig. 1*B*). For example, in our study the highest recognition confidence level (a rating of "6") was associated with the highest number of targets (92% of all "6" responses were to targets). Accordingly, activity in the MTL that is revealed in a contrast between high confidence judgments and low confidence judgments might reflect the difference between high and low confidence or it might reflect the difference between old items and new items regardless of confidence level.

Our next analysis sought to distinguish the effect of old and new stimuli from the effect of recognition confidence in the MTL. An ANOVA involving trial type (hits, misses, correct rejections, and false alarms) revealed four regions of significant activation: left temporopolar cortex (1,200 mm^3), left entorhinal cortex (280 mm^3), left hippocampus (3,864 mm^3), and right hippocampus (1,888 mm^3) (Fig. 2 *A*–*C*). Post-hoc paired *t tests* revealed that activity in left hippocampus, right hippocampus, and left entorhinal cortex was greater on trials when correct responses (i.e., confidence ratings of "4", "5", or "6") were made to targets (hits) than on trials when any other response was made (all *ps* <0.05). In the left temporopolar cortex, activity on trials when foils were incorrectly called old (false alarms) was less than

Table 1. Distribution of reaction times for memory confidence by old/new status (mean msec ± SEM)

	Old/new confidence rating					
	1	2	3	4	5	6
Targets	1750 ± 137	1853 ± 81	1919 ± 88	1823 ± 70	1631 ± 65	1360 ± 44
Foils	1598 ± 58	1722 ± 66	1857 ± 76	1890 ± 71	1759 ± 88	1545 ± 57

the activity on trials when any other response was made ($ps < 0.05$). In addition, in the left temporopolar cortex, activity in association with correct rejections was lower than activity in association with hits ($t[12] = 2.62$, $P < 0.05$) (Fig. 2*D*). The impulse response curves from these regions were orderly and confirm these findings (Fig. S1). Regions with significant activation in the whole brain analysis are listed in Table S2.

We next examined activity in the MTL regions that were active in the ANOVA contrast as a function of confidence level for the targets and foils separately (Fig. 2 *E* and *F*). Across the four confidence levels for targets (Fig. 2*E*), there was a positive linear trend in the left hippocampus ($F[1,12] = 42.72, P < 0.001$), in the right hippocampus ($F[1,12] = 15.20$, $P < 0.01$), and in the left entorhinal cortex ($F[1,12] = 12.54$, $P < 0.01$) and a marginal linear trend in the left temporopolar cortex ($F[1,12] = 4.49$, $P = 0.06$). Fig. 2*F* illustrates the response in the MTL to foils across confidence levels. Across the five confidence levels for foils, there was a significant negative linear trend in the left temporopolar cortex ($F[1,12] = 11.76$, $P < 0.01$) and in the left entorhinal cortex ($F[1,12] = 5.45$, $P < 0.05$). This linear trend was not evident in left or right hippocampus ($P > 0.20$).

Thus, in both the hippocampus and the parahippocampal gyrus activity increased in a linear fashion as confidence in recognition of the targets increased. In other words, both regions demonstrated a recognition signal, that is, activity was strongest when the recognition judgment was associated with the highest confidence and the highest accuracy. However, recognition confidence did not modulate activity in the hippocampus in response to foils. In contrast, in the temporopolar and entorhinal cortices, activity was modulated by recognition confidence in a manner consistent with a novelty signal, that is, activity was greatest for high-confidence new responses and activity decreased in a linear fashion with decreasing novelty.

Discussion

Participants performed a recognition memory task in the fMRI scanner for words that were studied immediately before scanning. Participants rated their recognition confidence for both old and new words on a 6-point recognition confidence scale. We performed two sets of analyses on the fMRI data from the MTL. The first set of analyses replicated what has been found previously in similar studies; namely, activity in the hippocampus bilaterally was low in association with confidence ratings of 1–5 and high in association with a confidence rating of 6 (3–5). The interpretation of these results is ambiguous because it is unclear whether activity was related to the confidence rating itself or to whether the stimulus was a target or a foil. The second set of analyses sought to address this ambiguity and found that activity for foils in the anterior parahippocampal gyrus was highest for foils judged as new with high confidence and that activity decreased as a function of confidence (a novelty effect). There was no novelty effect detected for foils in the hippocampus. For targets, activity in both the anterior parahippocampal gyrus and the hippocampus was lowest for targets that were judged to be new (misses), and activity in both these regions increased for hits as a function of increasing recognition confidence (a familiarity effect).

The finding of a familiarity effect in the hippocampus and parahippocampal gyrus for targets but not for foils indicates that this activity was related to the actual old/new status of an item rather than to participants' report of which items were old. That is, both targets and foils were sometimes declared to be old with high confidence, but this increased activity was related to the targets and not to the foils. This finding suggests that the brain "knew" the old/new status of the stimulus independently of the overt behavior of the participant. A similar finding has been observed previously in single-cell recordings in the monkey. Messinger et al. (15) recorded from inferior temporal (IT) cortex while monkeys performed a visual paired-associates task in which they saw a test image and then decided which of two images had been associated with the test image. Overall, 54% of sampled neurons responded to the correct image regardless of which image the monkey selected. In humans, Daselaar et al. (12) also identified a region in posterior hippocampus and parahippocampal cortex where activity was greater for old stimuli than for new stimuli regardless of the participant's behavioral response. The authors concluded that the posterior MTL detects an objective difference between old and new items and that this information does not always guide behavior. In a different study, activity in early visual cortex distinguished between old and new stimuli regardless of the overt behavioral response (16).

Our findings are consistent with these observations in humans and monkeys. Specifically, the response in the MTL can be modulated by the old/new status of the stimulus and does not always track the behavioral response of the participant. Accordingly, in fMRI studies, analyses that consider only the behavioral response and that combine target and foil trials together (such as the first set of analyses that we conducted here) can potentially mischaracterize the response in the MTL. The difficulty arises because combining targets and foils will usually result in there being different proportions of targets and foils across recognition confidence levels. When we combined targets and foils, activity in the MTL was low for the lower confidence levels (because of the high proportion of foils at these levels), and activity increased sharply for the higher confidence levels (because of the high proportion of targets at these levels). Previous studies that analyzed activity in relation to confidence ratings, while combining targets and foils, have obtained similar results (3, 4). Note that when Daselaar and colleagues (4) used the same dataset to compare activity for targets and foils independently of confidence ratings, they also observed differential responses in the posterior MTL to targets and foils (12). Accordingly, the effect reported in their first paper (4) may have been influenced by the relative proportions of targets and foils at each of the recognition confidence levels.

Note that the response in the hippocampus that we observed for targets increased monotonically with recognition confidence. This is not to say that the hippocampus was active for low-confidence decisions relative to misses or relative to baseline. Indeed, when we contrasted hits with confidence 4 or 5 against misses, we did not observe active regions in the hippocampus.

A number of previous studies have observed MTL activity in response to stimulus novelty (11, 17–19; for review, see 20). We observed a novelty effect within the anterior parahippocampal gyrus. That is, activity was highest when participants had high confidence that an item was new. This finding is consistent with electrophysiological (21) and neuroimaging studies (2, 22) that found higher activity in anterior MTL for novel relative to familiar stimuli. It should be noted, however, that we observed this effect only when we considered the foils separately from the targets. The response in this region to targets increased with increasing recognition confidence, an effect that eliminated the novelty response when targets and foils were considered together. Last, we did not observe a novelty effect in the hippocampus itself. It is possible that a novelty response in the hippocampus was attenuated by the fact that the stimuli used here (common English words) were all familiar before the experiment, and with such material one would not have expected strong novelty effects. It is also possible that only particular kinds of novelty (e.g., novelty in the associations between items) elicit hippocampal activity (23). In addition, the response in the hippocampus to foils could have been influenced by occasions when individuals noted that a specific foil was not presented at study ("recall-to-reject") or the response could be related to the encoding of novel stimuli during the retrieval phase.

Conclusion

We collected confidence ratings while participants performed a recognition memory test for words. When we analyzed activity in relation to old and new stimuli separately, we observed a novelty signal for foils in the anterior parahippocampal gyrus and a familiarity signal for targets in the anterior parahippocampal gyrus and in the hippocampus. These results indicate that activity in the MTL can sometimes reflect the old/new status of the test items rather than a participant's report of which items are old. Accordingly, the actual old/new status of stimuli, not just overt behavioral responses, need to be considered when analyzing and interpreting neuroimaging studies of recognition memory.

Methods

Participants. Thirteen right-handed volunteers (4 female; mean age = 29; range = 23–42) recruited from the University 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 >500 (mean = 573) obtained from the MRC Psycholinguistic Database (24). Half the words were assigned to six 60-word study lists, and half the words served as foils for the retrieval test. The assignment of words to the study and retrieval test conditions was randomized across participants. All words were presented in black font on a white background.

Procedure. Before scanning, participants made a pleasant/unpleasant rating for each of 360 study words (2.5-s presentation time) by pressing one of two marked buttons on a laptop computer keyboard (Fig. 1*A*). Participants were not informed that their memory for the words would be tested. The study session was divided into six equal blocks of 60 trials with short breaks between blocks.

Following the study session, participants took a memory test in the MRI scanner for the 360 target words and 360 foil words (Fig. 1*A*). Participants were scanned in 9 separate runs (≈2-min delay between runs), during which the 360 target words were presented at a rate of one word every 3.5 s. For each word, participants made an old/new recognition judgment on a 6-point scale (1 = ''sure new'', 2 = ''probably new'', 3 = ''guess new'', 4 = ''guess old'', 5 = ''probably old,'' and 6 = ''sure old'') during the 3.5-s presentation time using an MR-compatible button box. Participants were encouraged to use the entire 6-point scale. An odd/even digit task (25) was intermixed with word presentation and served as a baseline against which the hemodynamic response was estimated. For the digit task, participants saw a digit (1–8) for 1.75 s and indicated by button press whether the digit was odd or even. Digit task trials (104 trials per scan run) were pseudorandomly intermixed with the word presentation trials with the following constraints: each scan run began and ended with at least 12 digit trials, and all digit trials occurred in groups of 2, 4, or 6. The mean inter-trial interval was 5.1s (range = 0–10.5 s). Participants were given a short practice block before scanning to ensure that they understood the task and the button box.

fMRI Imaging. Imaging was carried out on a 3T GE scanner at the Center for Functional MRI (University of California at San Diego). Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (TR = 1,750 ms; 264 TRs/run; 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. Twenty-nine oblique coronal slices (slice thickness = 5 mm) were acquired perpendicular to the long axis of the hippocampus and covering the whole brain. Following the nine functional runs, high-resolution structural images were acquired using a T1-weighted IR-SPGR pulse sequence (24 cm field of view; 10 ° flip angle; TE = 3.7 ms; 166 slices; 1.4 mm slice thickness; matrix size = 256·256).

fMRI Data Analysis. fMRI data were analyzed using the AFNI suite of programs (26). Functional data were 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 TR immediately preceding and following the motion-contaminated TR. Behavioral vectors were created that coded each retrieval trial according to the memory confidence rating (1 through 6) and the old/new status of the stimulus. Trials in which there was no response during either the encoding task or during the subsequent recognition memory test (mean = 3.1 per participant) were modeled but then excluded from further analysis. Two separate models were created. The first model collapsed levels of confidence and old/new status of the stimuli into four categories: hits [correct ''old'' responses (4, 5, or 6) to a target], misses [incorrect ''new'' responses (1, 2, or 3) to a target], correct rejections [correct ''new'' responses (1, 2, or 3) to a foil], and false alarms [incorrect ''old'' responses (4, 5, or 6) to a foil]. The second model separated the responses to targets and foils according to confidence rating. Because of low numbers of high-confidence incorrect responses, some categories were combined to ensure that the numbers of trials in each condition were adequate for estimating the hemodynamic response. After combining, there were a total of nine behavioral vectors in the second model: responses of 1, 2, or 3 to targets (mean = 81.5 trials ± 11.4), responses of 4 to targets (46.2 ± 10.7), responses of 5 to targets (51.8 ± 7.6), responses of 6 to targets (206.0 ± 17.2), responses of 1 to foils (77.7 ± 11.9), responses of 2 to foils (99.4 ± 11.5), responses of 3 to foils (78.5 ± 9.1), responses of 4 to foils (58.8 ± 10.1), and responses of 5 or 6 to foils (43.5 ± 8.4). 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 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 versus baseline in each voxel for a given time point and for each of the trial types. This activity was summed over the expected hemodynamic response (0–15.75 s after trial onset) and taken as the estimate of the response to each trial type (relative to the digit task baseline).

Initial spatial normalization was accomplished using each participant's structural MRI scan to transform the data to the atlas of Talairach and Tournoux (27). Statistical maps were also transformed to Talairach space, resampled to 2 mm^3, and smoothed using a Gaussian filter (4 mm FWHM) that respected the anatomical boundaries of the several MTL regions defined for each individual participant (see below). Specifically, the smoothing was carried out within each of the anatomically defined MTL regions, but smoothing was not extended beyond the edges of these regions to prevent activity from one region (e.g., parahippocampal cortex) from being blurred into another, adjacent region (e.g., hippocampus). This was accomplished by creating a separate mask for each region, smoothing the data within that mask, and then recombining the smoothed data. The Talairach-transformed data were used in the whole-brain analyses.

A region of interest alignment technique was used to improve cross-participant alignment of the medial temporal lobe and thus increase statistical power for group analyses. The alignment technique used was conceptually similar to the region of interest large deformation diffeomorphic mapping technique (ROI-LDDMM) (28, 29) and was carried out using the diffeomorphic demons tool for MedINRIA software (ROI-Demons) (30). The first step in this approach is to define anatomical regions of interest for each subject. Anatomical regions of interest were manually segmented in 3D on the Talairach-transformed anatomical images for the hippocampus, temporal polar, entorhinal, perirhinal, and parahippocampal cortices on each side. Temporal polar, entorhinal, and perirhinal cortices were defined according to the landmarks described by Insausti et al. (31). The caudal border of the perirhinal cortex was defined as 4 mm caudal to the posterior limit of the gyrus intralimbicus as identified on coronal sections (31). The parahippocampal cortex was defined bilaterally as the portion of the parahippocampal gyrus caudal to the perirhinal cortex and rostral to the splenium of the corpus callosum (32). Using ROI-Demons, the anatomically defined ROIs for each individual participant were then used to normalize each subject's set of ROIs to a previously defined template for each structure (29). Diffeomorphic mapping techniques such as ROI-Demons have the advantage over other flat-mapping techniques that the spatial transformation of structures takes place so as to maintain the relationships between voxels. This transformation was then applied to the statistical maps, and all MTL analyses were performed on the ROI-Demons transformed data.

Following individual deconvolution analysis, individual subject parameter estimate maps were entered into group-level analyses and thresholded at a voxel-wise P value of $P = 0.03$. For the MTL analyses, group statistic maps were masked using the MTL template from the ROI-Demons alignment procedure 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 voxels was needed to be statistically meaningful ($P < 0.05$) (33, 34) within the volume of the MTL (minimum cluster extent of 33 contiguous voxels) and for the entire brain (minimum cluster extent of 104 voxels).

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