Cerebral Cortex Advance Access published January 29, 2008

Cerebral Cortex
doi:10.1093/cercor/bhm245

Dissociation between Explicit Memory and Configural Memory in the Human Medial Temporal Lobe

Alison R. Preston[1,2] and John D.E. Gabrieli[3]

[1]Center for Learning and Memory, [2]Department of Psychology, University of Texas at Austin, 1 University Station C7000, Austin, TX 78712-0805, USA and [3]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Using functional magnetic resonance imaging, the current study explored the differential mnemonic contributions of the hippocampus and surrounding medial temporal lobe (MTL) cortices to explicit recognition memory and configural learning. Using a task that required processing of repeated and novel visuospatial contexts across multiple trials, we examined MTL activation in relation to 3 forms of learning in a single paradigm: 1) context-independent procedural learning, 2) context-dependent configural learning, and 3) explicit recognition memory. Activations in hippocampus and parahippocampal cortex were associated with explicit memory, differentiating between subsequently remembered and forgotten repeated contexts, but were unrelated to context-dependent configural learning. Activations in regions of perirhinal and entorhinal cortex were associated with configural learning of repeated contexts independent from explicit memory for those contexts. Procedural learning was unrelated to activation in any MTL region. The time course of activation across learning further differed in MTL subregions with MTL cortex demonstrating repetition-related decreases and hippocampus repetition-related increases. These repetition effects were differentially sensitive to recognition with only activation in hippocampus and parahippocampal cortex tracking recognized items. These imaging findings converge with studies of amnesia and indicate dissociable roles for hippocampus in learning that supports explicit recognition and for anterior MTL cortex in configural learning.

Keywords: configural, explicit, hippocampus, medial temporal lobe, memory

Introduction

A major goal of cognitive neuroscience is characterization of the essential mnemonic roles of the hippocampus and surrounding medial temporal lobe (MTL) structures, the entorhinal, perirhinal, and parahippocampal cortices. MTL damage results in profound impairment to declarative memory (Cohen and Squire 1980) measured by explicit memory tasks, such as recall or recognition that require conscious awareness of episodic experience (Tulving 1983; Graf and Schacter 1985). Performance is preserved, however, on implicit tests of procedural memory in which learning is measured as experience-induced performance changes unrelated to awareness or explicit memory (Squire 1992; Gabrieli 1998). The anatomical organization of the MTL region, however, suggests that distinct regions within the MTL may differentially mediate different types of memory representations and the behaviors that rely upon them. Animal research has inspired hypotheses and computational models positing a fundamental distinction between hippocampal mediation of relational memory and MTL cortical mediation of configural memory (Eichenbaum 1994; Eichenbaum et al. 1996; Cohen et al. 1997). Here, we used functional magnetic resonance imaging (fMRI) with a spatial contextual learning paradigm (Chun and Jiang 1998) to test the hypothesis that relational and configural memory would be associated, respectively, with hippocampal and MTL cortical activation in the human brain.

It has been proposed that the hippocampus, at the apex of the MTL hierarchy, may have the unique ability to integrate information across multiple domains forming relational or conjunctive representations (Marr 1971; McClelland et al. 1995; Eichenbaum and Cohen 2001; O'Reilly and Rudy 2001; Norman and O'Reilly 2003). Such representations bind together distinct elements of experience, maintaining the compositionality of the elements and organizing them according to their interrelations (Eichenbaum et al. 1996). The elemental nature of these representations is proposed to support pattern completion mechanisms that allow for a partial cue to activate an entire hippocampal representation (O'Reilly and Rudy 2001). Relational or conjunctive representations are thought to underlie the mnemonic flexibility that allows for novel use of memories, including conscious recollection during recall and recognition. Animal experimentation has demonstrated the essential role of the hippocampus for the flexible, inferential use of learned information (Bunsey and Eichenbaum 1996; Dusek and Eichenbaum 1997). In neuroimaging with humans, the hippocampus has been associated specifically with relational memory (Heckers et al. 2004; Preston et al. 2004) and with conscious recollection for recognition memory (Eldridge et al. 2000).

In contrast to relational representations formed by hippocampus, MTL cortex has been proposed to form configural representations (Eichenbaum 1994; Eichenbaum et al. 1996; Cohen et al. 1997). Configural representations have been described as having fused structures such that the elements of an event are bound into a unitized memory trace. Because of their unitized nature, pattern completion mechanisms cannot operate on such representations. Partial cues (i.e., elements of the original event) will not result in the reactivation of a stored memory trace so that expression of configural representations may be tightly bound to the original learning task. Such configural representations are not capable of being flexibly addressed by a novel set of cues and, therefore, cannot support conscious recollection. In humans, however, there is no direct evidence as yet that configural learning processes are mediated by MTL cortices or that relational and configural learning can be dissociated within the MTL. Further, it is unknown as to whether separable MTL cortical regions, the anterior or perirhinal and entorhinal cortices and the posterior or

parahippocampal cortex, play similar or different roles in configural memory.

In addition to hypothesized representational differences, hippocampus and MTL cortical regions are proposed to have different learning rates. The hippocampus has been proposed to support the rapid acquisition of information in 1 trial (Nakazawa et al. 2003). In contrast, it has been proposed that MTL cortex gradually acquires memory traces across multiple learning trials, whereby statistical co-occurrences of elements are abstracted across time (O'Reilly and Rudy 2001). In humans, there is limited direct investigation of learning rates across time and how they may differ in MTL subregions.

The learning of spatial contextual information offers an opportunity to dissociate relational (explicit) and configural memory processes in the MTL and to examine learning rates in different MTL structures. A visuospatial contextual learning task (Chun and Jiang 1998) requires participants to perform a visual search of spatial contexts to locate a target among a field of perceptual distractors. Context-dependent learning is reflected as greater decreases in reaction time for contexts repeated throughout the experiment relative to novel contexts (contextual cueing), suggesting that learning of spatial configurations in repeated contexts facilitates visual search (Chun and Jiang 1998). Importantly, such facilitation occurs independent of explicit recognition for repeated contexts (Chun and Jiang 2003). Indeed, the facilitation occurs when participants have no explicit memory for the visuospatial contexts (i.e., are at chance on explicit recognition tests). This task also offers a measure of procedural memory as reaction times for target identification decrease with training for both novel and repeated contexts (Chun and Jiang 1998). Visual search of novel contexts is not facilitated by previous exposure to individual contexts as each novel context is presented only once throughout the experiment. Thus, improved visual search for novel contexts reflects a form of procedural memory, which may rely on statistical learning mechanisms that are not context specific.

The 3 kinds of memory assessed within this single paradigm (procedural learning, contextual cueing, and explicit memory for visuospatial contexts) have been examined in amnesic patients with either large MTL lesions encompassing the hippocampus and MTL cortex or focal injury to the hippocampus. Amnesic patients with large MTL lesions demonstrate intact procedural learning in this task but fail to demonstrate contextual cueing and explicit recognition (Chun and Phelps 1999; Manns and Squire 2001). The failure of amnesic patients with large MTL lesions to demonstrate contextual cueing is striking because this cueing occurs implicitly in healthy people (i.e., this form of learning is measured indirectly by reaction time performance and occurs in the absence of explicit memory for the visuospatial contexts). This and other findings, (Barense et al. 2005; Lee et al. 2005; Daselaar, Fleck, Prince, Cabeza 2006; Schnyer et al. 2006) challenge the standard view of MTL function in memory by demonstrating that MTL regions contribute to memory performance that occurs in the absence of explicit awareness. Furthermore, amnesic patients with focal hippocampal damage demonstrate intact procedural and context-dependent learning despite recognition memory deficits (Manns and Squire 2001). This patient finding suggests that MTL cortex supports context-dependent (configural) learning that cannot support explicit recognition memory and that the hippocampus is required for the relational memory representation that supports explicit recognition memory.

These patient findings motivate the hypotheses that 1) hippocampus mediates learning processes essential for the formation of explicit memory (relational memory) for visuospatial contexts, 2) MTL cortex mediates learning processes essential for configural memory for visuospatial contexts (learning visuospatial configurations across repetitions would underlie the contextual cueing effect), and 3) non-MTL regions mediate procedural learning underlying facilitation of novel visuospatial contexts. These hypotheses predict that fMRI activation in hippocampus would be associated specifically with explicit memory for visuospatial contexts, MTL cortex specifically with contextual cueing, and non-MTL regions specifically with procedural learning. Furthermore, learning-related activations in distinct MTL regions can be tracked across the course of the experiment due to the multitrial nature of the contextual cueing task.

Relevant neuroimaging studies have examined MTL activations for the encoding and retrieval of explicit or declarative memories. Visuospatial contextual learning differs fundamentally from those studies, however, because encoding and retrieval are intermingled in a design where the same stimuli are repeated multiple times during learning. Each re-presentation of a specific visuospatial context, for example, constitutes both an encoding trial for subsequent presentations and a retrieval trial for prior presentations. With this caveat, prior neuroimaging studies suggest a possible dissociation between anterior MTL cortices (perirhinal and entorhinal cortex) and posterior or parahippocampal cortex. Previous neuroimaging studies have demonstrated parahippocampal activation that predicts later recognition memory performance (Brewer et al. 1998; Wagner et al. 1998) with such parahippocampal responses often tracking activation in hippocampal regions (Davachi et al. 2003; Ranganath et al. 2003; Kirwan and Stark 2004). Thus, the anterior aspects of MTL cortex may be a more likely location for a learning process that can be dissociated from the hippocampus.

Materials and Methods

Participants

Twenty-five healthy, right-handed volunteers participated in the experiment for payment after giving informed consent in accordance with a protocol approved by the Stanford Institutional Review Board. Data from 23 participants were included in the analyses (age 18–30 years, mean = 20.4 ± 0.52 years; 10 males, 15 females) and data from 2 participants were excluded due to problems with data acquisition.

Materials and Design

During scanning, stimuli were generated by a Macintosh G3 (Apple, Cupertino, CA) computer and back projected via a magnet-compatible projector onto a screen that could be viewed through a mirror mounted above the participant's head. Participants responded with an optical button held in their right hand and responses were recorded by a computer interfaced with the optical switch using the PsyScope button box (Cohen et al. 1993).

The task was a modified version of the contextual cueing task described by Chun and Phelps (1999). On each trial, participants saw 11 colored L-shaped distractors and 1 colored, 90°-rotated T-shaped target (Fig. 1). Elements of the contexts were arranged in an 8 by 6 grid of possible locations. Two sets (A and B) of 600 unique contexts were generated. For each unique set of contexts, 12 of the 48 grid locations were randomly selected as possible target positions. The 12 possible

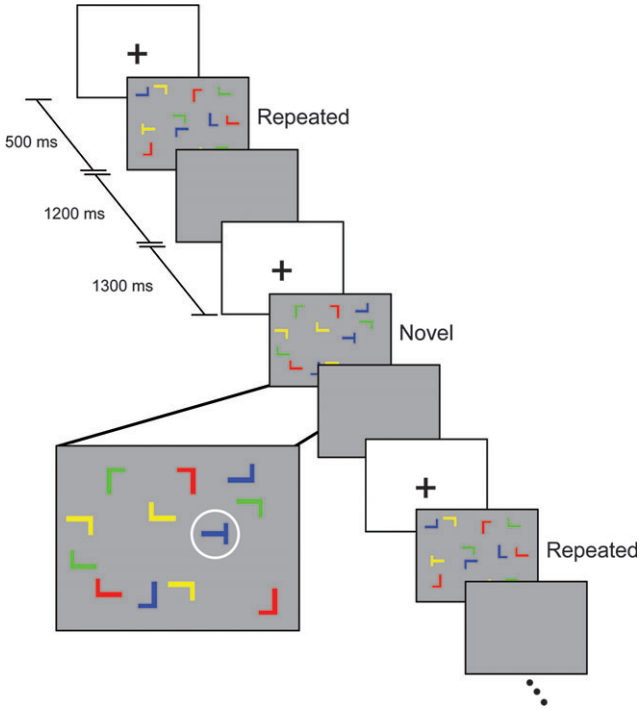

Figure 1. Stimuli and trial structure of the contextual cueing task. During scanning, participants performed a visual search task indicating whether the base of a target T pointed left or right. Twelve repeated contexts were presented 20 times throughout scanning. Novel contexts were seen only once in the experiment.

target positions selected for each set were distinct from one another. For each context, the target was randomly selected from the set of possible color (4) and position (12) combinations. Targets appeared equally in all possible locations, and each color was assigned to an equal number of targets. The positions for the 11 remaining distractor items were randomly selected from the remaining 36 possible locations. The orientation and color of each distractor were randomly determined with the constraint that there were 3 distractors of each color in each context.

Sets A and B were then assigned as either "repeated" or "novel" contexts for each participant and counterbalanced across participants. Independently for each participant, 12 of the 600 contexts from the repeated set were selected as the repeated contexts for that participant. These 12 repeated contexts were each displayed 20 times each across the entire experiment for a total of 240 repeated presentations. For each repetition, the direction of the target during the 12 repeated contexts was randomly determined, but all other aspects of the contexts were maintained across repetitions. Similarly for each participant, 240 different contexts were randomly selected from the novel set to serve as the novel contexts for that participant. Each novel context was displayed only once throughout the entire experiment.

Across 4 event-related functional runs, participants saw a total of 480 contexts, 60 repeated contexts (12 contexts repeated 5 times) and 60 novel contexts per run. Each trial lasted 3 s and consisted of a fixation cross that signaled the beginning of the trial (500 ms), the presentation of the context (1200 ms), and an intertrial interval (1300 ms). Participants were instructed to locate the T-shaped target as quickly as possible by pressing 1 of 2 keys to indicate the direction the base of the T was pointing. Participants could make a response at any point during the stimulus presentation period and the intertrial interval. To determine the order of trials for each participant, each run was divided into 5, 24-trial blocks consisting of the 12 repeated contexts and 12 novel contexts. The order of repeated and novel trials within each block was then randomly determined. Intermixed with repeated and novel trials in each run were 120, 3-s null fixation trials during which no contexts were presented and no response was made.

Approximately 20 min after scanning, participants performed a surprise recognition memory test to measure their explicit memory for the repeated contexts. Participants were presented with the 12 repeated contexts from scanning along with 12 new foil contexts selected from the set of novel contexts and not previously seen during scanning. Participants were instructed to indicate whether each presented context was "old" or "new" by responding with 1 of 2 keys. The recognition test was self-paced. Each context was presented for 2 s followed by a variable length response period. Participants could make their response during the presentation of the context or in the period following its presentation. After a participant made a response, the next context was displayed after a 500-ms fixation period.

Imaging Procedure

Whole-brain imaging data were acquired on a 3.0-T Sigma MRI system (GE Medical Systems, Milwaukee, WI). Prior to functional imaging, T_2-weighted flow-compensated spin-echo anatomical images (time repetition [TR] = 4500 ms; echo time [TE] = 85 ms) were acquired in 30 contiguous 6-mm coronal slices. Functional images were acquired with the same slice locations as the anatomical images using a T_2^*-weighted 2-dimensional gradient echo spiral pulse sequence (Glover and Lai 1998) (TR = 2000 ms; TE = 30 ms; 1 interleave; flip angle = 75°; FOV = 24 cm; 64 × 64 voxels). A total of 1,088 functional volumes were acquired for each participant over 4 sessions. Six discarded volumes (a total of 12 s) were collected at the beginning of each scan session to allow for T_1 stabilization.

Imaging Analyses

Image preprocessing and statistical analyses were performed using SPM99 (Wellcome Department of Cognitive Neurology). Images were corrected to account for the differences in slice acquisition times by interpolating the voxel time series using sinc interpolation and resampling the time series using the center slice as a reference point. Functional volumes were then realigned to the first volume in the time series to correct for motion. A mean T_2^*-weighted volume was computed during realignment, and the T_2-weighted anatomical volume was coregistered to this mean functional volume. The T_2-weighted anatomical volume was then spatially normalized into common stereotactic space using a standard template brain from the Montreal Neurological Institute series (Cocosco et al. 1997). The spatial transformations calculated during the normalization of the anatomical volume were then used to normalize the functional volumes. After normalization, the functional volumes were resampled to 2 mm^3 voxels and smoothed with an 8-mm isotropic Gaussian kernel.

For individual participants, differences between repeated and novel contexts were assessed using the general linear model (Friston et al. 1995). Regressor functions were constructed by convolving 2 covariates modeling the conditions (repeated and novel) with a synthetic hemodynamic response function. Individual participant data were then analyzed using a fixed effects model (Friston et al. 1994), and linear contrasts were performed to generate a SPM(t) map representing differences in brain activation between the 2 kinds of contexts. Contrast images comparing repeated and novel contexts were generated in the individual participant analysis and then analyzed across participants using a mixed-effects general linear model, treating participants as a random effect allowing for population inference (Holmes and Friston 1998). Unless otherwise noted, a standard statistical threshold adopted in numerous previous fMRI studies (5 or more contiguous voxels exceeding an uncorrected threshold of $P < 0.001$) was used to identify significant voxels for the group analysis. As in previous studies (Eldridge et al. 2000; Davachi and Wagner 2002; Bunge et al. 2004), a slightly more lenient threshold of $P < 0.005$ (5 voxel extent) was adopted to assess activation in the MTL given the lower signal-to-noise ratio often observed in this region (Ojemann et al. 1997; Schacter and Wagner 1999).

A second statistical model was calculated to isolate differences between repeated contexts based on later memory performance. For this model, regressor functions were constructed by convolving 3 covariates modeling recognized repeated contexts (repeated hits), unrecognized repeated contexts (repeated misses), and novel contexts.

This model served as a basis for region of interest (ROI) analyses interrogating the relationship between brain activation and later recognition memory performance. To further assess brain regions associated with recognition memory, we subdivided participants into 2 groups based on corrected hit rate. Participants with recognition performance at or near chance levels were included in a "without-recognition" group. Those participants who demonstrated above-chance recognition memory performance were included in a "with-recognition" group. This division of groups based on recognition performance was used as a between-subjects factor in ROI analyses.

Regression analyses were performed weighting individual contrast images by behavioral measures of performance on the scanned contextual cueing task and the postscan recognition memory test. These analyses were used to isolate brain regions associated with procedural learning for the novel contexts, context-dependent configural memory, and explicit recognition associated with the repeated contexts. These analyses seek to address how different MTL subregions may mediate performance in the contextual cueing task.

Specifically, to investigate brain regions associated with procedural learning contrast images for novel contexts relative to baseline were weighted by behavioral measures of performance across all participants. Procedural learning is hypothesized to occur for both novel and repeated contexts. However, additional contextual learning may occur during presentation of repeated contexts that may rely on brain regions that are distinct from those that contribute to procedural learning. Thus, by limiting our analysis of procedural learning to novel contexts, we seek to isolate brain regions associated with procedural learning independent of contextual cueing. Similarly, contrast images for repeated relative to novel contexts were weighted by the contextual cueing performance of all participants to isolate brain regions associated with context-dependent memory. The contrast of repeated and novel contexts was selected to uniquely isolate those regions related to contextual cueing while controlling for brain regions associated with procedural learning that would be common to both repeated and novel trials.

Regression analyses examining activation associated with recognition memory performance were calculated only for those participants who demonstrated above-chance recognition memory in terms of corrected hit rate by weighting contrasts between repeated and novel contexts by recognition performance. The average activation for novel trials served as a baseline for observing repetition-related increases or decreases in activation that were associated with later recognition. An alternative regression analysis that included all participants yielded the same associations between explicit memory and MTL activations. We report the regression analyses limited to those participants with above-chance recognition memory performance due to the difficulty in the interpretation of variance in memory performance at or near chance levels.

ROI analyses were performed for regions identified by the regression analyses. For each participant, percent signal change was extracted for 3 conditions: novel contexts and repeated contexts split by whether they were later recognized (repeated hit) or unrecognized (repeated miss) on the postscan memory test. Integrated percent signal change was determined by calculating the area under the curve for the period of time 2–10 s poststimulus onset for each condition across the entire experiment. These data were first submitted to a mixed-effects analysis of variance (ANOVA) with context type (repeated and novel) as a within subjects factor and recognition memory group (with or without recognition) as a between-subjects factor. A second ANOVA with subsequent memory as a within subjects factor and recognition performance as a between-subjects factor was performed to assess how each ROI was modulated by memory for the repeated contexts. Planned comparisons were also performed to assess pairwise differences between each of the conditions. Correlation analyses were also performed for each ROI to assess how activation in specific regions was associated with procedural learning, contextual cueing, and recognition memory. Correlation analyses examining the relationship between brain activation and recognition memory were limited to a group of subjects demonstrating above-chance recognition memory performance. For procedural learning and contextual cueing, such correlation measures were calculated across all participants as well as separately for participants with and without recognition memory. For MTL structures, additional interaction analyses assessed differences between regions across the 3 different conditions. Localization of MTL activations was assessed using standard anatomical landmarks (Amaral and Insausti 1990; Insausti et al. 1998). Group averages of activations in small MTL structures can be misleading, so activations from individual participants' anatomical images were given precedence in determining the locations of MTL activations.

Additional ROI analyses were performed to assess how activation of different MTL regions was sensitive to repetition across learning. A third statistical model was created that modeled novel trials as well as repetition effects for the repeated trials. Each of the 12 repeated stimuli were displayed 20 times throughout learning. To increase the statistical power of these analyses, 10 regressors were created for the repeated items that collapsed across 2 TR points. Thus, the first and second repetitions were treated as a single condition, the third and fourth trials and so on. For each participant, percent signal change was extracted for each repetition regressor and integrated percent signal change was determined for 10 repetition time points. These data were submitted to a mixed-effects ANOVA with repetition and memory outcome (repeated hits and repeated misses) as within subjects factors and recognition memory (with or without recognition) as a between-subjects factor.

Results

Contextual Cueing Performance

Participants were highly accurate when detecting the direction of the target during the search task (mean = 97.5%, standard error [SE] = 0.51%). They were significantly more accurate for repeated (mean = 97.90%, SE = 0.43%) than novel (mean = 97.10%, SE = 0.65%) contexts, indicating greater facilitation in accuracy with the repetition of a context ($t_{22} = 2.11$, $P < 0.05$). As previously observed (Chun and Jiang 1998; Chun and Phelps 1999), performance on the search task displayed 2 components. Overall reaction times decreased across the functional runs for both types of context demonstrating procedural learning that was independent of context (Fig. 2*a*; main effect of scan session, $F_{1,3} = 39.60$, $P < 0.001$). In addition, participants' reaction times decreased more for repeated contexts than novel contexts, demonstrating a form of memory dependent on context (main effect of context type, $F_{1,3} = 13.34$, $P < 0.001$). Context-dependent facilitation that significantly differed from 0 was observed by the second functional run of the experiment (Fig. 2*a*; mean = 62 ms; SE = 21.8; $t_{22} = 3.46$, $P < 0.005$), but was not observed during the first functional run (mean = 16 ms; SE = 26.3; $t_{22} = 1.21$, $P = 0.24$). Significant context-dependent facilitation was also observed during the third (mean = 65 ms; SE = 22.6; $t_{22} = 4.12$, $P < 0.001$) and fourth (mean = 54 ms; SE = 20.5; $t_{22} = 3.69$, $P < 0.001$) runs. However, the magnitude of such facilitation during the latter 3 functional runs did not differ (all pairwise *P*values > 0.10). Thus, although the additional reaction time facilitation for repeated trials emerged only with repeated exposure (functional run × context type interaction, $F_{1,3} = 5.78$, $P < 0.001$), such context-dependent learning emerged in the second block and remained at the same level in the third and fourth blocks.

To further assess context-dependent facilitation effects, a measure of contextual cueing was calculated for each participant by computing the difference in reaction times for repeated and novel contexts during runs 3 and 4 (Chun and Jiang 1998; Chun and Phelps 1999). This measure of contextual cueing also revealed greater reaction time facilitation for repeated relative to novel contexts during the latter half of the

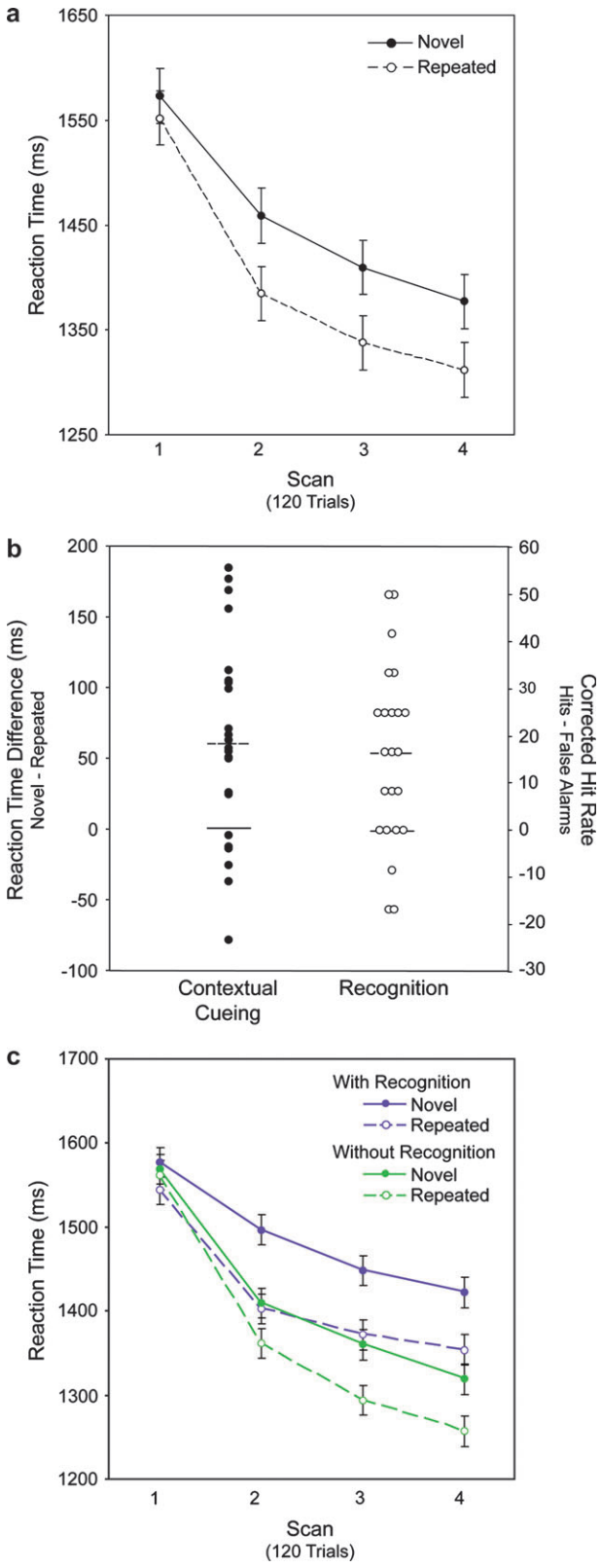

Figure 2. Behavioral performance on the contextual cueing and postscan recognition memory tasks. (*a*) Plotted are the reaction times during the contextual cueing task for repeated and novel contexts for each of the 4 functional runs. With increased exposure, participants' visual search performance was facilitated for the repeated relative to the novel contexts. (*b*) Scatter plots of contextual cueing (filled circles) and recognition memory (open circles) scores for each participant. Black lines represent no reaction time difference for the contextual cueing task and chance recognition memory performance. The dotted lines represent mean contextual cueing and corrected hit rate. (*c*) Contextual cueing split by recognition memory group (with recognition in purple, without recognition in green). Contextual cueing, indexed by the reaction time difference between novel (solid lines) and repeated (dashed lines) contexts did not differ based on later recognition memory performance. However, there was a trend for procedural learning measures to differ between the 2 recognition memory groups with those participants without recognition memory demonstrating faster reaction times for novel trials across learning relative to those with recognition.

experiment (mean difference = 61 ms, SE = 14.9; $t_{22} = 4.10$, $P < 0.001$). These results suggest that participants encoded the visual contexts of the repeated displays resulting in faster performance on the search task for these contexts. However, the amount of contextual cueing observed was variable across participants (Fig. 2*b*; min = –77.9 ms, max = 184.7 ms), with some participants demonstrating large measures of contextual cueing and others demonstrating no reaction time facilitation for repeated contexts.

Procedural Learning

To calculate a measure of procedural learning independent of contextual cueing, we examined improvements in performance for the novel contexts reflected in the negative slope of the reaction time function for these contexts across functional runs (mean = –66.2 ms, SE = 10.2). The degree of procedural learning, as measured by the slope of the reaction time function for novel contexts, varied across participants (min = –266.4 ms, max = –22.5). This measure of procedural learning was not correlated with measures of contextual cueing ($R^2 = 0.01$, $P > 0.10$).

Explicit Recognition Memory Performance

Recognition memory performance on the postscan memory test was low (hits = 62.7%, SE = 3.3%; false alarms = 46.7%, SE = 3.5%), but significantly above chance (corrected hits = 15.9%, SE = 4.0%; $t_{22} = 4.03$, $P < 0.001$). Measures of d′ also revealed above-chance performance on the recognition memory test (mean = 0.56, SE = 0.18; $t_{22} = 3.19$, $P < 0.005$).

Similar to contextual cueing performance, participants demonstrated variability in recognition memory performance (Fig. 2*b*; corrected hits: min = –16.7%, max = 50.0%). To investigate the relationship between declarative memory for and facilitated search of the repeated contexts in the contextual cueing task, the correlation between corrected hit rate and contextual cueing score was calculated. There was little correlation between contextual cueing and recognition memory performance ($R^2 = 0.01$, $P > 0.10$). However, a null correlation between 2 different measures of performance, in this case a measure of recognition accuracy and a reaction time difference score, does not necessarily imply functional independence. To further assess the relationship between contextual cueing and later recognition memory, contextual cueing scores were calculated separately for repeated contexts that were later recognized and those that were not recognized. Contextual cueing measures for repeated contexts did not significantly differ based on later recognition status ($t_{22} = 1.36$, $P > 0.19$). Thus, learning in the contextual cueing paradigm was not related to successful recognition of repeated contexts. Recognition performance was also not correlated with procedural learning associated with novel contexts ($R^2 = 0.04$, $P > 0.10$).

Additionally, the relationship between contextual cueing and recognition memory performance was examined by dividing participants into 2 groups based on corrected hit rate. Ten participants demonstrated poor recognition memory performance that was at or near chance levels (less than 8.5% corrected hits). A second group of 13 participants demonstrated above-chance recognition memory performance at levels greater than 16% corrected hits. Both corrected hit rate and d′ measures of recognition memory differed between groups ($F_{1,21}$ = 47.63, P < 0.001 and $F_{1,21}$ = 15.11, P < 0.001, respectively). Recognition memory performance in the poor recognition group did not significantly differ from chance (mean corrected hits = –1.7%, SE = 3.0%; t_9 = 0.56, P > 0.10), and this group was identified as the without-recognition group. Recognition memory performance in the second group of participants was significantly above chance (mean corrected hits = 29.5%, SE = 3.2%; t_{12} = 9.17, P < 0.001), and this group was identified as the with-recognition group.

To investigate the effects of subsequent recognition memory on contextual cueing performance, we performed a 1-way ANOVA with recognition memory performance as a factor, which revealed that contextual cueing scores did not differ significantly between those participants with (mean = 72 ms, SE = 21.7) and without recognition (mean = 46 ms, SE = 19.5; $F_{1,21}$ = 0.73, P = 0.40). In addition, a 2-way repeated measures ANOVA assessing contextual cueing effects across runs with recognition performance as a between-subjects factor and functional run as a within subjects factor, revealed a significant effect of run on measures of contextual cueing (Fig. 2*c*; $F_{1,3}$ = 4.61, P < 0.01), but no significant effects of recognition memory ($F_{1,1}$ = 1.89, P > 0.10), or the interaction between subsequent recognition and run ($F_{1,3}$ = 0.73, P > 0.10). Thus, there were similar levels of context-dependent facilitation across time within the recognition memory groups. Further, reaction time differences between repeated and novel contexts during the first and fourth functional runs did not differ as a function of later recognition memory ($F_{1,21}$ = 1.05, P > 0.10, and $F_{1,21}$ = 0.90, P > 0.10, respectively). Thus, later recognition memory performance was unrelated to measures of contextual cueing performance.

A 1-way ANOVA with recognition memory as a factor revealed a trend for the effect of recognition performance on procedural learning scores ($F_{1,21}$ = 2.98, P = 0.10). Participants without recognition memory demonstrated greater levels of procedural learning (mean = –85 ms, SE = 20.6) than those with recognition (mean = –51.3 ms, SE = 7.4). Further, a 2-way repeated measures ANOVA with recognition memory as a between-subjects factor and functional run as a within subjects factor, revealed a significant effect of run on procedural learning ($F_{1,3}$ = 33.88, P < 0.001) with reaction times to novel contexts decreasing across run. The main effect of recognition memory performance also trended toward significance ($F_{1,1}$ = 3.26, P = 0.09), as did the interaction between recognition performance and run (Fig. 2*c*; $F_{1,3}$ = 2.52, P < 0.10), demonstrating greater reductions in reaction times to novel trials across run in participants without recognition relative to those with recognition. Separate examination of reaction times for the novel contexts during the first and fourth functional runs revealed no difference between recognition groups during the first run ($F_{1,21}$ = 0.05, P > 0.10), but a significant difference in reaction times to novel contexts in the fourth run ($F_{1,21}$ = 4.23, P < 0.05) with participants without recognition (mean = 1301 ms, SE = 44.2) demonstrating faster reaction times than those with recognition (mean = 1422 ms, SE = 38.7). Thus, superior recognition memory for repeated contexts was associated with inferior procedural learning.

MTL Cortical Activation Related to Contextual Cueing

Regression analyses were performed to explore how activation in MTL regions was associated with behavioral indices of performance (Table 1). The first of these regression analyses identified regions where the difference between novel and repeated contexts was modulated by contextual cueing performance across all participants. Two regions in left entorhinal/perirhinal cortex demonstrated patterns of activation associated with measures of contextual cueing (Fig. 3*b*,*c*; –20, –4, –42 and –14, –10, –30). The former of these regions (–20, –4, –42) was also revealed by direct contrasts of repeated and novel contexts (see Supplementary Results online). In the latter entorhinal/perirhinal region (–14, –10, –30), differences in activation between repeated and novel contexts were observed only when performance on the contextual cueing task was taken into account. Similar patterns of activation were not

Table 1
Regions associated with behavioral performance

Region	MNI coordinates			Number of voxels	*Z* score	Relation to behavior
	x	*y*	*z*			
Recognition (with recognition)						
Superior temporal gyrus (BA 41)	48	−14	−12	147	4.32	3
	−46	−10	−18	17	3.32	3
Superior temporal gyrus (BA 38)	54	20	−28	39	3.73	3
Superior parietal lobule (BA 7)	14	−54	76	342	3.69	3, 4a–b
	−20	−32	84	69	3.61	2a–c, 3
	30	−76	54	27	3.26	3, 4a–b
Inferior parietal lobule (BA 7)	−32	−80	30	392	3.62	3
Inferior parietal lobule (BA 40)	60	−40	20	23	3.45	3, 4a–b
	−54	−50	22	13	3.24	3
Cerebellum	22	−42	−54	99	3.54	2a–c, 3, 4a–b
Middle frontal gyrus (BA 6)	30	4	36	53	3.32	3
Superior occipital gyrus	26	−84	48	50	3.22	3
Cingulate (BA 32)	18	8	42	16	3.22	3
Inferior frontal gyrus (BA 44)	−34	8	16	12	3.19	3
	54	14	20	49	3.17	3
Thalamus	18	−30	8	25	3.04	3
Hippocampus[a]	−30	−20	−12	65	3.05	3, 4a
	34	−26	−8	48	2.99	3, 4a
Parahippocampal cortex[a]	−18	−34	−20	44	2.87	3, 4a–b
	18	−40	−16	30	2.74	3, 4a–b
Contextual cueing						
Inferior parietal lobule (BA 39/40)	56	−64	50	51	3.67	1c, 2a–c
	−60	−46	42	20	3.20	1c, 2a–c
	−54	−64	38	28	3.17	1c, 2a–c
	60	−58	40	21	3.11	1c
	54	−78	28	22	3.00	1c
Cuneus (BA 19)	14	−96	22	19	3.09	1c
Entorhinal/perirhinal cortex[a]	−14	−10	−30	5	2.72	1a–c
	−20	−4	−42	5	2.68	1a–c
Procedural learning						
Precuneus	10	−58	28	32	3.81	2c
Inferior frontal gyrus (BA 46)	−56	38	4	47	3.56	2c
Insula	32	−14	20	14	3.45	2b
Superior frontal gyrus (BA 9)	8	64	32	12	3.35	2b
Cerebellum	18	−42	−20	6	3.31	2c
	−16	−36	−24	15	3.29	2c

Note: 1. Correlation with contextual cueing in (a) all participants, (b) those with recognition, and (c) those without recognition. 2. Correlation with procedural learning in (a) all participants, (b) those with recognition, and (c) those without recognition. 3. Correlation with recognition memory in participants with recognition. 4. Differentiation between repeated hits and misses in (a) with-recognition and b) without-recognition groups. BA, Brodmann area.
[a]A priori ROI identified at P < 0.005 (uncorrected).

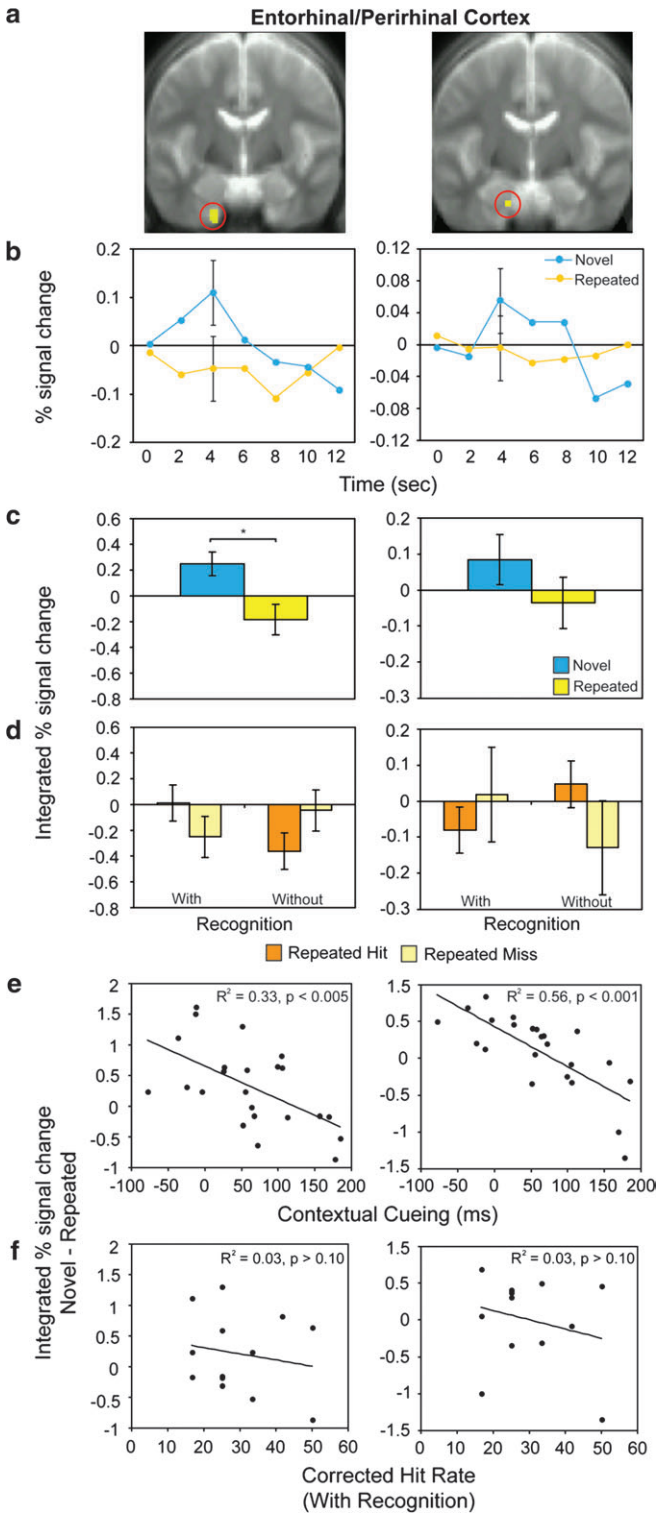

Figure 3. Activation in left entorhinal/perirhinal cortex (−18, −10, −44 and −14, −10, −30) correlated with contextual cueing performance. (*a*) ROI displayed on group-averaged anatomical images. (*b*) Time course of activation in each ROI for novel (blue) and repeated (yellow) contexts. (*c*) Integrated percent signal change in ROI for novel and repeated contexts. (*d*) Integrated percent signal change for repeated contexts by split by memory performance on the postscan recognition test for both with- and without-recognition memory participants: repeated hit (orange) and repeated miss (light yellow). (*e*) Integrated percent signal change difference for novel relative to repeated contexts plotted by contextual cueing score, and (*f*) corrected hit rate for participants with recognition memory. Asterisks indicate significant differences.

observed in right entorhinal or perirhinal cortex even at more liberal thresholds of $P < 0.05$.

Activation in both regions of left entorhinal/perirhinal cortex was significantly correlated with measures of contextual cueing performance across all participants (Fig. 3*e*; $R^2 = 0.33$, $P < 0.005$ and $R^2 = 0.56$, $P < 0.001$, respectively). In these regions, greater reaction time facilitation for repeated contexts relative to novel contexts was associated with greater activation for repeated relative to novel trials. In contrast, failure to demonstrate facilitation for repeated contexts was associated with greater activation for novel relative to repeated trials. This differential pattern of activation suggests that successful learning on the contextual cueing task may rely on modulation of the response in left entorhinal/perirhinal cortex. When assessed separately by recognition memory group, this relationship between activation in left entorhinal/perirhinal cortex and contextual cueing was observed in participants with ($R^2 = 0.36$, $P < 0.05$; $R^2 = 0.58$, $P < 0.005$) and without ($R^2 = 0.25$, $P < 0.05$; $R^2 = 0.47$, $P < 0.05$) recognition. An additional multiple regression analysis was performed to assess how variability in each of these regions tracked variability contextual cueing performance. Stepwise multiple regression demonstrated that activation in both entorhinal/perirhinal regions accounted for a significant amount of variance in contextual cueing scores. A single-region regression model produced a R^2 value of 0.56 ($P < 0.001$). A 2-region model increased the R^2 to 0.65 ($P < 0.001$). The regression coefficients for each region were also significant ($t = 4.30$, $P < 0.001$; $t = 2.28$, $P < 0.05$), suggesting that each of these regions uniquely contribute to contextual cueing.

Although activation in left entorhinal/perirhinal cortex was associated with greater levels of contextual cueing, response in these regions was not correlated with measures of procedural learning across all participants ($R^2 = 0.02$, $P > 0.10$; $R^2 = 0.03$, $P > 0.10$) or within either recognition group (all $P > 0.10$). In addition, activation in these regions was not correlated with performance on the recognition memory test in participants with recognition (Fig. 3*f*; $R^2 = 0.03$, $P > 0.10$; $R^2 = 0.06$, $P > 0.10$). To further interrogate the relationship between activation in these regions and recognition memory group, a 2-way repeated measures ANOVA examined the difference between repeated contexts that were later recognized and those that were unrecognized across both recognition groups. Activation in these regions did not differentiate between repeated contexts that were later recognized relative to those that were not recognized ($F_{1,21} = 0.01$, $P > 0.10$; $F_{1,21} = 0.07$, $P > 0.10$), nor was there a main effect of recognition group ($F_{1,21} = 0.30$, $P > 0.10$; $F_{1,21} = 0.01$, $P > 0.10$) or an interaction between recognition group and activation for each type of repeated context (Fig. 3*d*; $F_{1,21} = 1.08$, $P > 0.10$; $F_{1,21} = 0.86$, $P > 0.10$). Thus, activation in left entorhinal/perirhinal cortex was unrelated to measures of procedural learning or recognition memory accuracy.

MTL Activation Related to Explicit Recognition Memory

Additional regression analyses were performed to isolate MTL regions associated with recognition memory performance in participants with recognition memory. These analyses revealed regions in bilateral hippocampus (−30, −20, −12 and 34, −26, −8) and bilateral parahippocampal cortex (−18, −34, −20 and 18, −40, −16) that were associated with recognition memory performance (Fig. 4 and Table 1). In hippocampal regions, the

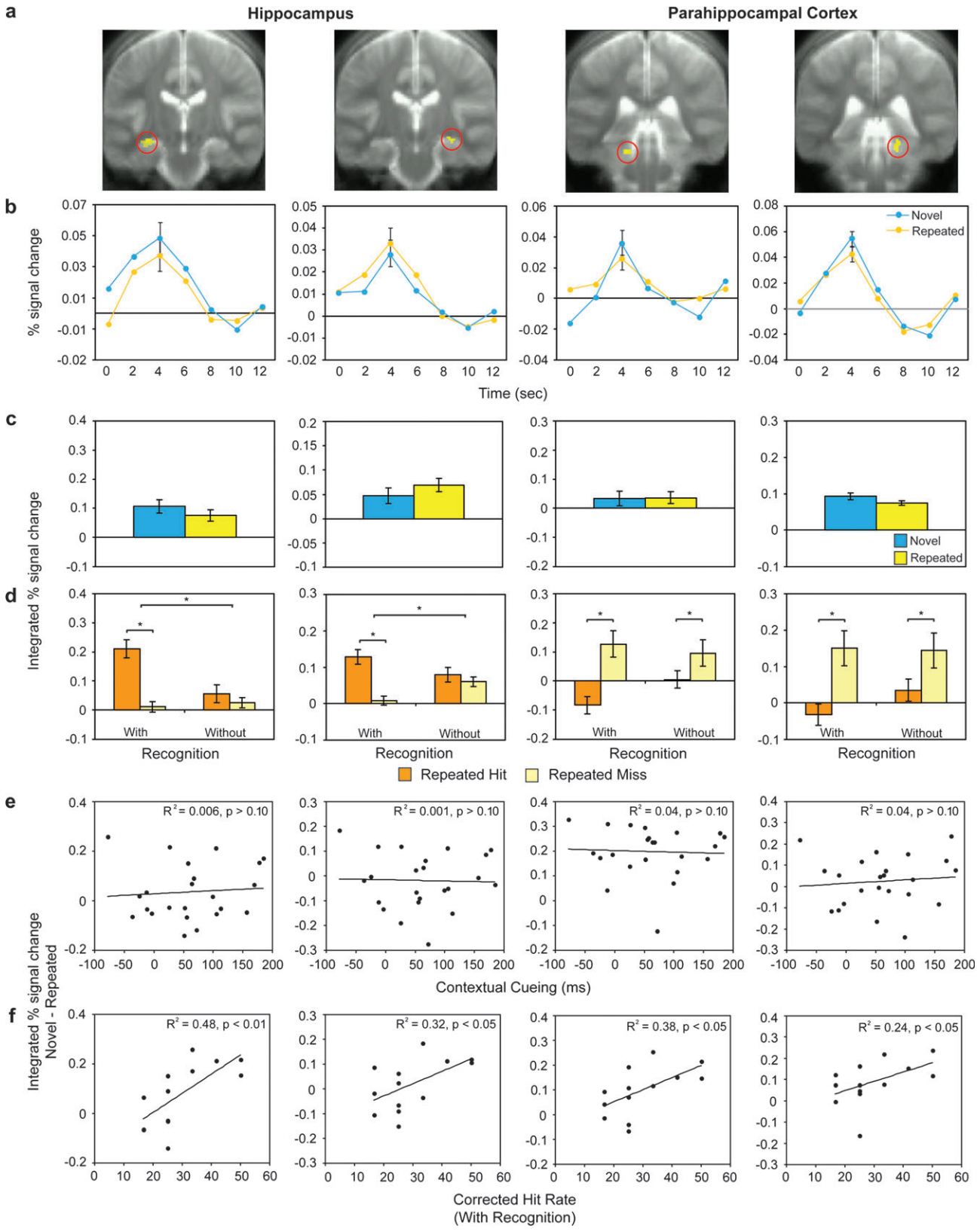

Figure 4. Activation in bilateral hippocampus (−30, −20, −8 and 34, −26, −8) and parahippocampal cortex (−18, −34, −20 and 18, −40, −16) correlated with recognition memory performance. (*a*) ROI displayed on group-averaged anatomical images. (*b*) Time course of activation in each ROI for novel (blue) and repeated (yellow) contexts. (*c*) Integrated percent signal change in ROI for novel and repeated contexts. (*d*) Integrated percent signal change for repeated contexts by split by memory performance on the postscan recognition test for both with- and without-recognition memory participants: repeated hit (orange), repeated miss (light yellow). (*e*) Integrated percent signal change difference for novel relative to repeated contexts plotted by contextual cueing score, and (*f*) corrected hit rate for participants with recognition memory. Asterisks indicate significant differences.

observed correlations with corrected hit rate in participants with recognition (left hippocampus: $R^2 = 0.48$, $P < 0.01$; right hippocampus: $R^2 = 0.32$, $P < 0.05$) revealed that higher levels of successful recognition were associated with greater activation for novel relative to repeated contexts in these regions (Fig. 4*f*). In addition, activation in these hippocampal regions predicted later memory performance for repeated contexts across all participants, demonstrating greater activation for repeated contexts that were later recognized relative to unrecognized repeated contexts (left hippocampus: $F_{1,21} = 8.31$, $P < 0.01$; right hippocampus: $F_{1,21} = 11.39$, $P < 0.005$). Activation in left hippocampus was modulated by recognition performance with greater activation observed in participants with recognition than those without recognition ($F_{1,21} = 5.47$, $P < 0.05$) as well as a significant interaction between activation for recognized versus unrecognized repeated contexts and recognition memory group (Fig. 4*d*; $F_{1,21} = 4.389$, $P < 0.01$). Participants with recognition demonstrated a greater difference between recognized and unrecognized repeated contexts than those without recognition. No main effect of recognition memory was observed in right hippocampus ($F_{1,21} = 0.00$, $P > 0.10$), but there was a significant interaction between activation for recognized versus unrecognized repeated contexts and the 2 recognition groups (Fig. 4*d*; $F_{1,21} = 7.00$, $P < 0.05$) demonstrating a similar pattern to that observed in left hippocampus. Thus, by a number of measures, hippocampal activation was associated with recognition accuracy.

The pattern of activation in hippocampus significantly differed from that of entorhinal/perirhinal cortex (context type × region, $F_{1,21} = 4.85$, $P < 0.05$), suggesting that these regions contributed to different aspects of learning in this task. In addition, activation in these hippocampal regions was not associated with measures of contextual cueing when assessed across all participants (Fig. 4*e*; left hippocampus: $R^2 = 0.01$, $P > 0.10$; right hippocampus: $R^2 = 0.00$, $P > 0.10$) or separately for the recognition groups (all $P > 0.10$). Nor was the response in these regions associated with measures of procedural learning when assessed for all participants (left hippocampus: $R^2 = 0.06$, $P > 0.10$; right hippocampus: $R^2 = 0.02$, $P > 0.10$) or separately for the recognition groups (all $P > 0.10$).

Similar to regions in hippocampus, activation in bilateral parahippocampal cortex was correlated with recognition memory performance in participants with recognition (Fig. 4*f*; left parahippocampal cortex: $R^2 = 0.34$, $P < 0.05$; right parahippocampal cortex: $R^2 = 0.24$, $P < 0.05$). Greater activation was observed for novel relative to repeated contexts with increasing levels of recognition memory. These regions also distinguished between repeated contexts based on their mnemonic outcome. However, unlike hippocampal regions, regions in bilateral parahippocampal cortex demonstrated greater activation for repeated contexts that were unrecognized relative to those that were recognized (left parahippocampal cortex: $F_{1,21} = 5.27$, $P < 0.05$; right parahippocampal cortex: $F_{1,21} = 4.15$, $P < 0.05$). These regions did not demonstrate main effects of recognition memory performance (left parahippocampal cortex: $F_{1,21} = 0.56$, $P > 0.10$; right parahippocampal cortex: $F_{1,21} = 0.76$, $P > 0.10$) nor an interaction between recognition group and activation for recognized and unrecognized repeated contexts (Fig. 4*d*; left parahippocampal cortex: $F_{1,21} = 0.81$, $P > 0.10$; right parahippocampal cortex: $F_{1,21} = 0.27$, $P > 0.10$).

The pattern of response in parahippocampal cortex differed from that observed in entorhinal/perirhinal cortex, which demonstrated reductions in response to repeated stimuli relative to novel stimuli regardless of memory outcome (context type × region, $F_{1,21} = 5.23$, $P < 0.01$), and differed from that observed in hippocampus which also successfully predicted memory for repeated contexts but demonstrated the greatest activation for repeated contexts that were later recognized (context type × region, $F_{1,21} = 18.45$, $P < 0.001$). Further, activation in bilateral parahippocampal cortex was not associated with contextual cueing in either recognition group or across all participants (Fig. 4*e*; all $P > 0.10$). Similarly, activation in this region was unrelated to measures of procedural learning across all participants or when assessed separately by recognition group (all $P > 0.10$).

An additional multiple regression analysis assessed how variance in corrected hit rate in participants with recognition could be explained by activation in the bilateral regions of hippocampus and parahippocampal cortex. Including all regions in the regression did not account for additional variance beyond that explained by inclusion of the left hippocampus as a single factor ($R^2 = 0.48$, $P < 0.01$; significance for individual regression coefficients: left hippocampus, $t = 3.19$, $P = 0.009$; right hippocampus, $t = 0.74$, $P > 0.10$; left parahippocampal cortex, $t = 1.05$, $P > 0.10$; right parahippocampal cortex, $t = 0.87$, $P > 0.10$). This result suggests that differences in left hippocampal activation accounted for the greatest proportion of variance in recognition memory performance within the group of participants with recognition. We also performed a multiple regression all participants. When participants without recognition were included in this analysis, activation in left hippocampus and left parahippocampal cortex both significantly explained variance in corrected hit rate ($R^2 = 0.64$, $P < 0.001$; significance for individual regression coefficients: left hippocampus, $t = 2.58$, $P = 0.02$; right hippocampus, $t = 0.42$, $P > 0.10$; left parahippocampal cortex, $t = 4.72$, $P = 0.004$; right parahippocampal cortex, $t = 1.37$, $P > 0.10$). These results suggest that variance in activation in both left hippocampus and left parahippocampal cortex accounts for variance in recognition performance across all participants. The inclusion of participants whose recognition performance was at or near chance levels introduces factors related to response bias. Near chance performance differences between corrected hit rates may solely arise from response biases rather than difference in the strength of memory.

Whole-Brain Regions Associated with Behavioral Performance

Further regression analyses were performed to assess the relation between brain activation and procedural learning by assessing how activation for novel contexts relative to baseline differed as a function of procedural learning scores for all participants. This analysis failed to isolate any MTL regions whose activation varied as a function of procedural learning even at a more liberal threshold of $P < 0.05$, suggesting that this form of learning is mediated by other brain regions. Outside the MTL, regression analyses revealed several brain regions, including regions in frontal, parietal, and occipital cortices as well as cerebellum, whose activation was modulated by behavioral performance including procedural learning (Table 1). Regions in left inferior frontal gyrus, right superior frontal gyrus, right insula, right precuneus, and bilateral cerebellum were associated with procedural learning. Further regression analyses

revealed regions of bilateral inferior parietal lobule and a region in right cuneus demonstrated patterns of activation that varied as a function of contextual cueing performance. These regions demonstrated greater activation for repeated relative to novel contexts for the greatest levels of contextual cueing. Several regions throughout the brain were associated with recognition memory performance in the above-chance recognition memory group (Table 1). Observed correlations with recognition memory revealed that higher levels of successful recognition were associated with greater activation for novel relative to repeated contexts in these regions. Each of the regions identified by the regression analyses was submitted to a ROI analysis to further investigate how activation in these regions was related to behavioral measures of performance and memory outcome for repeated contexts. The results of those ROI analyses are summarized in Table 1.

Repetition Effects in MTL Regions across Learning

For each MTL region where activation was associated with behavioral performance, either contextual cueing or later recognition memory, we further assessed how activation in each region was sensitive to the repetition of repeated stimuli across learning. A repeated measures ANOVA with repetition, memory outcome, and recognition group as factors revealed that activation in the regions of left entorhinal/perirhinal cortex that were associated with contextual cueing was sensitive to repetition ($F_{9,189}$ = 2.30, P < 0.05 and $F_{9,189}$ = 2.05, P < 0.05) but not memory outcome, recognition memory group, or the interaction between factors (all P values >0.10). These regions of entorhinal/perirhinal cortex demonstrated a rapid decrease in activation from first block of 2 repetitions to the second block (Fig. 5*a*), and this effect was observed in both recognition memory groups regardless of later memory outcome (repeated hits and repeated misses). Activation during the first repetition block demonstrated significantly greater activation than all other blocks (all P < 0.05), with all other blocks demonstrating no significant differences from one another.

Activation in bilateral hippocampal regions associated with recognition memory group also demonstrated sensitivity to the presentation of repeated contexts across time (Fig. 5*b*) but only in participants with recognition memory for the repeated contexts that were later recognized (repetition × memory outcome × group, left hippocampus: $F_{9,189}$ = 2.94, P < 0.05; right hippocampus: $F_{9,189}$ = 2.31, P < 0.05). In participants with recognition, activation gradually increased across learning but only for repeated items that were later recognized as demonstrated by a significant linear trend across time that interacted with memory outcome (left hippocampus: $F_{1,12}$ = 27.17, P < 0.001; right hippocampus: $F_{1,12}$ = 8.43, P < 0.01).

Activation in bilateral parahippocampal cortex also demonstrated changes in activation that were sensitive to repetition effects (Fig. 5*c*). Activation in these regions was modulated by memory outcome (repetition × memory outcome, left parahippocampal cortex: $F_{9,189}$ = 3.23, P < 0.001; right parahippocampal cortex: $F_{9,189}$ = 5.96, P < 0.001) but not recognition group (repetition × memory outcome × recognition group, left parahippocampal cortex: $F_{9,189}$ = 0.09, P > 0.10; right parahippocampal cortex: $F_{9,189}$ = 0.70, P > 0.10). For both recognition memory groups, significant linear decreases across repetition were observed in bilateral parahippocampal cortex

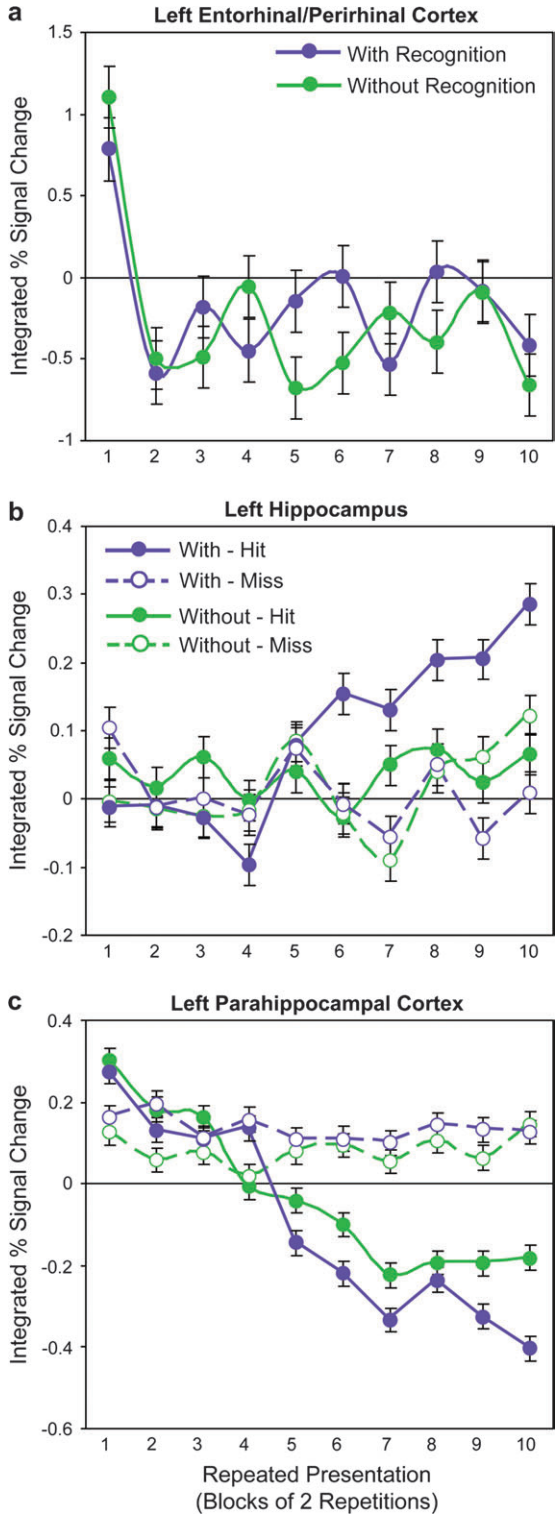

Figure 5. Time course of activation across stimulus repetition. (*a*) Activation in left entorhinal/perirhinal region (−18, −10, −44) plotted across presentation of repeated times with each point representing 2 stimulus repetitions. Activation in this region decreased significantly after the first 2 repetitions but demonstrated no further decreases across continued repetition and did not differ for participants with (purple) or without (green) recognition. (*b*) Activation in left hippocampus (−30, −20, −8) plotted across repetition for participants with (purple) and without (green) recognition and split by memory performance: repeated hits (solid) and repeated misses (dashed). Activation in left hippocampus gradually increased with stimulus repetition but only for hits and only in participants with recognition. (*c*) Activation in left parahippocampal cortex (−18, −34, −20) demonstrated gradually decreasing activation for repeated hits with stimulus repetition in both recognition memory groups.

but only for those repeated contexts that were later recognized (left parahippocampal cortex: $F_{1,21} = 16.70$, $P < 0.001$; right parahippocampal cortex: $F_{1,21} = 32.52$, $P < 0.001$).

Discussion

The current study examined contributions of specific MTL regions to 3 kinds of memory on a visuospatial search task that included repeated and novel visuospatial contexts: 1) explicit memory for repeated contexts measured by a postscan recognition test; 2) context-dependent configural memory measured by faster response time for repeated relative to novel contexts; and 3) context-independent procedural learning measured by faster response times for novel contexts. Participants exhibited all 3 forms of memory, with considerable variation in the magnitude of memory effects across participants. Hippocampal and parahippocampal activation was associated specifically with explicit memory for repeated contexts in a group of participants with above-chance recognition memory performance. Entorhinal/perirhinal activation was related specifically to configural memory for repeated contexts in both participants with and without above-chance recognition memory. There was no involvement of MTL structures in procedural learning for novel contexts. Activations associated with procedural learning were found in other regions, including the cerebellum and frontal cortex.

Hippocampal Activation Related to Explicit Recognition

The observed hippocampal activation suggests that hippocampus selectively mediated a form of learning that resulted in explicit memory for repeated contexts. Activation in bilateral hippocampus correlated with recognition memory performance in participants with recognition memory above chance, with greater activation associated with superior recognition memory performance. In addition, bilateral hippocampal activation was greater for recognized than unrecognized repeated contexts, similar to previous findings demonstrating hippocampal activation that predicted subsequent memory performance (Kirchhoff et al. 2000; Otten et al. 2001; Davachi and Wagner 2002; Strange et al. 2002; Kirwan and Stark 2004). This activation difference for repeated contexts based on subsequent recognition was greater in participants with recognition memory than in participants without recognition, suggesting that hippocampal involvement in this task is specifically linked to explicit recognition.

Activation in hippocampus was not associated with context-dependent configural memory or procedural learning, further supporting the specific link between hippocampal processing and explicit memory in this task. However, there was a trend for participants with recognition memory to demonstrate less procedural learning than participants without recognition, suggesting the possibility for competition between memory systems that support the declarative and procedural learning of this task (see also Poldrack et al. [2001]). The engagement of hippocampal mechanisms in support of later recognition memory performance may have adversely affected processing in other brain regions that support procedural learning in this task leading to less procedural learning. Conversely, those participants without recognition who demonstrate faster reaction times for visual search may spend less time processing the stimuli even with fixed presentation times that may result in poor recognition memory performance. Perhaps, greater procedural learning reduced the variability of stimulus encoding that enhanced recognition memory for specific patterns. These possibilities highlight the importance of future study assessing how the MTL memory system, and specifically hippocampus, interacts with other memory systems in the performance of this task.

The finding of significantly above-chance recognition memory in this paradigm contrasts with previous studies of the contextual cueing paradigm during which participants failed to explicitly recognize the repeated contexts above chance (Chun and Jiang 1998, 2003; Chun and Phelps 1999; Manns and Squire 2001). Participant age may have influenced the difference from previous findings as our participants were younger than those in at least 2 studies (Chun and Phelps 1999; Manns and Squire 2001). Another potentially important difference between the current imaging study and previous behavioral studies is the constant stimulus duration during both initial learning and later recognition utilized in the current study that may have led participants to adopt a more explicit behavioral strategy when performing the visual search task than participants in previous behavioral versions of the task leading to greater recognition performance. However, above-chance recognition accuracy has been found in 1 group in a behavioral study after a number of exposures similar to the current study (Manns and Squire 2001).

Hippocampal activation associated with explicit recognition demonstrated sensitivity to the repeated exposure of visuospatial contexts but in a way that interacted with memory outcome for repeated contexts and recognition memory performance across groups. In the above-chance recognition memory group, activation in hippocampal regions increased linearly for repeated contexts that were later recognized with increasing exposure to those contexts. Repetition-sensitive effects in hippocampus were not observed in participants without recognition or for the repeated contexts that were not later recognized in participants with recognition. Recent electrophysiological findings have observed hippocampal neurons that act as either familiarity or novelty detectors by increasing their firing rate in response to familiar and novel stimuli respectively after a single learning exposure (Rutishauser et al. 2006). Differences between these electrophysiological findings and our current data may result, in part, from differences in the spatial resolution of the 2 techniques. Many neurons contribute to activation at the voxel level; thus, rapid increases and decreases in the firing rate of single neurons are not observable at the level of anatomical detail available in the current data. The current findings suggest that across a population of hippocampal neurons, activation gradually increased with exposure to repeated items that were later remembered in the group of participants with recognition.

This observation of increasing hippocampal activation with repeated exposure that interacts with later explicit memory relates to a study examining hippocampal activation during a transitive inference paradigm (Greene et al. 2006). In this study, hippocampal activation increased with repeated exposure to pairs of visual stimuli (e.g., BC, CD) that served as premise pairs for a later inferential judgment (i.e., BD). Further, hippocampal activation late in training predicted later inferential performance at test for only a group of high performing participants.

Together with this finding, our results suggest that participants who successfully recruit the hippocampus during initial

learning may perform better on explicit tests of recognition memory than those participants who do not recruit the hippocampus. In addition, the time course of hippocampal activation in these successful participants tracked later memory for specific items with later recognized items demonstrating learning-related increases relative to unrecognized items. The dynamics of repetition-sensitive effects in participants with recognition also raise interesting questions of how recognition performance–related activation in this region is related to awareness, and more specifically, how the emergence of awareness is related to the gradually increasing activation observed in hippocampus. By combining online measures of the awareness of stimulus repetition with analyses examining the time course of hippocampal activation across such repetition, future study may better examine how activation in hippocampus tracks the emergence of awareness and the subjective experience of memory. Comparison between activation during an online measure of awareness and postscan tests of recognition may elucidate how the timing of such tests affects brain activation. Further, online measures may be necessary to rule out differences in retention intervals between our measures of contextual cueing and recognition that may impact the observed regional differences associated with these forms of learning.

Parahippocampal Activation Related to Explicit Recognition

Similar to hippocampus, activation in bilateral parahippocampal cortex was associated with recognition memory performance in participants with recognition, with greater activation associated with superior recognition memory performance. However, activation in parahippocampal cortex differed from activation in hippocampus in 2 important ways. First, activation in parahippocampal cortex demonstrated reduced activation for those repeated contexts that were later recognized relative to those that were not recognized. This reduction in parahippocampal activation was sensitive to the amount of repetition demonstrating a gradual linear decrease across exposure of those repeated contexts that were later recognized but not for unrecognized repeated contexts.

Second, unlike hippocampus, the pattern of activation in parahippocampal cortex did not differ between participants with and without recognition. Repetition decreases for repeated contexts that were later recognized were observed in both groups, and the time course of the reduction in activation across repetition did not differ between the groups. Such repetition-related reductions have been previously observed in MTL cortical regions in both electrophysiological (Brown and Aggleton 2001) and neuroimaging data (Henson and Rugg 2003; Gonsalves et al. 2005). Such reductions have been referred to as "repetition suppression" and have been hypothesized to serve as a basis for discriminating between familiar and novel items. Moreover, decreased activation in MTL cortex has been observed for hits relative to misses, indicating that these effects relate to memory perception rather than the actual history of the item (Weis, Klaver, et al. 2004; Weis, Specht, et al. 2004; Gonsalves et al. 2005).

In contrast to the repetition-related decreases observed in the current study, other neuroimaging studies have demonstrated greater activation in parahippocampal cortex during both encoding (Brewer et al. 1998; Wagner et al. 1998; Davachi et al. 2003; Ranganath et al. 2003; Kirwan and Stark 2004) and retrieval (Cabeza et al. 2001; Cansino et al. 2002; Daselaar, Fleck, Cabeza 2006) that is related to successful recognition memory performance, with such activation often tracking hippocampus (Davachi et al. 2003; Ranganath et al. 2003; Kirwan and Stark 2004). However, the contextual cueing paradigm differs fundamentally from the methods employed in these studies. During learning as the repeated contexts are represented, both encoding and retrieval processes are likely to be at work. In addition, recognition memory in the current study was assessed only for those highly repeated contexts rather than novel stimuli used in previous work.

Anterior MTL Cortical Activation Related to Contextual Cueing

Within MTL, only activation in entorhinal/perirhinal cortex was associated with individual differences in context-dependent memory regardless of later recognition memory performance and did not differ for recognized and unrecognized repeated contexts. This finding converges with a study in which perirhinal activation was associated with extraction of abstract relations implemented by a hidden rule during training on a serial reaction time task (i.e., greater activation associated with priming or skill learning) (Rose et al. 2002). In combination, these 2 findings suggest that perirhinal cortex may support some forms of configural memory that are unrelated to explicit recognition. The effects observed in anterior MTL cortex were left lateralized, and similar patterns of activation were not observed in right anterior MTL cortex even at more liberal thresholds. In a neuroimaging study examining implicit category learning of novel visuospatial patterns, category learning was associated with left-lateralized activations (Seger et al. 2000), so activation in the present study may reflect left-hemisphere specialization for representations of the repeated visuospatial contexts.

Further analyses revealed that activation in entorhinal/perirhinal cortex decreased with repeated exposure to visuospatial contexts. However, the time course of this reduction differed from that observed in parahippocampal cortex highlighting important differences between regions within MTL cortex as well as differences between entorhinal/perirhinal cortex and hippocampus. Activation in entorhinal/perirhinal cortex significantly decreased after the first 2 exposures and further repetition did not influence response in this region. The time course of this activation reduction mirrored the context-dependent behavioral response that demonstrated repetition-related reaction time facilitation during the second functional block that remained constant during the third and fourth blocks. The repetition effects observed in this region were not modulated by either memory outcome for repeated contexts (i.e., hits versus misses) or by recognition memory performance (i.e., with- and without-recognition groups) further distinguishing this region from both hippocampus and parahippocampal cortex. These rapid reductions in anterior MTL cortical activation with repeated exposure converge with electrophysiological data demonstrating reduced firing rates in this region after a single presentation (Brown and Xiang 1998). These findings are also interesting in the context of computational models of MTL function that suggest that MTL cortex may require multiple learning trials to gradually abstract the statistical co-occurrence of elements (Norman and O'Reilly 2003). The rapid decrease of activation in anterior MTL cortex suggests that under some conditions,

MTL cortical regions may rapidly form a representation of an event (in this case a visuospatial context) that can serve behavioral performance (in this case contextual cueing). However, in the current study, representation in anterior MTL cortex may be configural in nature and thus limited in behavior that is served, whereby only facilitated visual search performance for the repeated contexts is supported but not later explicit recognition.

Whole-Brain Regions Associated with Procedural Learning

Procedural learning was unrelated to any measure of MTL activation, which is consistent with extensive literature demonstrating intact procedural learning with large MTL lesions (Squire 1992; Gabrieli 1998). Activations in several brain regions outside of MTL were related to procedural learning including regions in frontal cortex and cerebellum, which have been linked to procedural memory in lesion (Gomez-Beldarrain et al. 1998, 1999) and neuroimaging studies (Eliassen et al. 2001; Poldrack et al. 2001). Procedural learning as measured in this study is not context dependent as the visual search of novel contexts could not be facilitated by previous exposure to individual contexts as each novel context is presented only once throughout the experiment. Instead, improved performance on novel trials may rely on visuospatial probabilistic learning mechanisms. In the current study, a limited set of locations served as target locations for novel and repeated contexts. A limited set of target locations enhanced the need for participants to learn the configuration of elements within the repeated contexts rather than focusing on specific individual target locations during these contexts. However, this aspect of the task design may help to explain the type of procedural learning exhibited for the novel contexts. Across trials, participants may learn to direct attention to the set of target locations as they carry a high probability of containing a target on each individual trial regardless of whether a trial is novel or repeated thus facilitating search on both types of trials. Such probabilistic learning of visuospatial locations has been previously demonstrated to facilitate performance on visual search tasks with faster performance observed for high probability visuospatial locations relative to low probability or random locations (Miller 1988; Geng and Behrmann 2005).

Organization of Memory Functions in the MTL

The present findings converge with prior studies of amnesic patients examining how MTL damage affects performance on the contextual cueing task. First, procedural learning was not associated with MTL activation, consistent with observations of intact procedural learning on this task with MTL damage (Chun and Phelps 1999; Manns and Squire 2001). Second, explicit recognition was associated selectively with hippocampal activation, a finding consistent with impaired explicit memory with focal hippocampal damage (Zola-Morgan et al. 1986; Rempel-Clower et al. 1996; Stark et al. 2002; Stark and Squire 2003; Squire et al. 2004). Third, configural memory for visuospatial contexts was associated selectively with MTL cortex, a finding consistent with patient evidence that large MTL lesions including the MTL cortex impair such configural memory, but that focal hippocampal lesions that spare MTL cortex also spare configural memory on this task (Chun and Phelps 1999; Manns and Squire 2001). Indeed, this is a strong convergence of lesion and imaging findings.

The imaging findings extend knowledge of the mnemonic organization of the MTL in 2 important ways beyond findings from the amnesia studies. First, configural memory was associated specifically with structures of the anterior MTL, namely perirhinal and entorhinal cortices. The amnesic patients had large lesions that encompassed many MTL structures, including parahippocampal cortex, which was not associated with contextual cueing in the imaging findings. Thus, the imaging data provide more precise anatomical candidates within the MTL for the mediation of visuospatial configural learning. In addition, the findings highlight important processing differences within MTL cortex, with anterior and posterior regions of MTL cortex mediating different aspects of the task. Whereas activation in anterior MTL cortex was associated with contextual cueing and decreased rapidly with repetition of visuospatial contexts, parahippocampal activation was associated with recognition memory and demonstrated gradually decreasing activation with repetition.

Second, the findings suggest a dissociation within MTL between contextual cueing and explicit memory in this paradigm. Previous findings from amnesic patients revealed only a single dissociation, where large MTL lesions impaired contextual cueing and focal hippocampal lesions did not. A single dissociation cannot distinguish between 2 alternative possibilities 1) that explicit learning is more difficult than configural learning and thus involves all components of the MTL, whereas configural learning can be accomplished with just some components of the MTL or 2) that learning mechanisms underlying configural and explicit memory are discretely related to the MTL cortex and hippocampus, respectively. The imaging findings are most compatible with a double dissociation between configural learning being mediated by anterior MTL cortices and explicit learning being mediated by hippocampus. In addition, the amnesia findings speak only to MTL contributions to learning, whereas the imaging results identified non-MTL regions associated with procedural learning, contextual cueing, and explicit recognition that presumably interact with MTL structures to mediate task performance.

Memory theories typically focus on distinctions between 2 types of learning, for example, explicit and implicit, or declarative and nondeclarative. The dichotomous relation between these forms of learning centers on their differential reliance on conscious awareness of experience and integrity of hippocampus and surrounding MTL structures. Our findings suggest a third category of learning that is context dependent (i.e., relies on learning spatial relations in repeated contexts) does not depend on explicit recognition, and is not related to hippocampal processing, but rather processing in anterior MTL cortex. The theoretical interpretation of our findings depends on the conceptualization of the type of representation that supports this form of context-dependent memory. Contextual cueing cannot reflect learning of specific target locations as the same locations were used in novel and repeated contexts. Nor can it reflect learning of specific context-response associations because target orientation was varied across repeated contexts. One possibility is that the global spatial layout of repeated contexts are learned. However, using the current paradigm, it has been shown that learning occurs for contexts formed by target and adjacent (rather than distant) distractors and that context-dependent learning is supported by both individual associations and more

abstract relations between targets and nearby distractors (Jiang and Wagner 2004).

MTL cortical structures are proposed to support such configural memory representations that integrate elements of an experience into fused representations (Eichenbaum 1994; Cohen et al. 1997). Because of their fused nature, such representations may be expressed only in the original learning task, are not flexibly addressable using novel cues different from the original learning, and may be unavailable to conscious awareness. In the current study, activation in anterior MTL cortex may reflect formation of fused configural representations of repeated contexts that facilitate visual search performance but cannot be accessed in the later recognition memory task. In contrast, relational representations formed by hippocampus are thought to separately code event elements, maintaining compositionality of elemental representations, and organizing them in terms of their relationships (Eichenbaum et al. 1996). This representational capacity is proposed to underlie the critical and unique role of the hippocampus in conscious, flexible use of learned information (Bunsey and Eichenbaum 1996; Reber et al. 1996; Dusek and Eichenbaum 1997; Heckers et al. 2004; Preston et al. 2004). The nature of hippocampal representation may allow elements of experience to be combined in new ways to address novel situations, and in the current paradigm, such hippocampal representations formed during visual search may extend beyond the original implicit learning experience allowing for later conscious recognition of repeated contexts. Our findings further expand these theories of MTL memory function by highlighting differences in the function of different MTL cortical structures. In our study, activation in entorhinal, perirhinal, and parahippocampal cortices contributed to different aspects of task performance and demonstrated different time courses of activation across stimulus repetition suggesting that these regions function to support memory in different ways and should not be considered as a functional unit (e.g., Eichenbaum et al. 1996).

The present study suggests that there may be a double dissociation between configural memory processes mediated by anterior MTL cortex, which integrate elements of experience into fused representations, and explicit memory processes mediated by hippocampus, which organizes elements of experience flexibly according to their interrelations. The specific association between hippocampus and explicit memory is consistent with a growing body of evidence demonstrating that learning processes that require awareness, from subjective recollection to illusory memories to trace conditioning, are hippocampally dependent. The observed association between activation in anterior MTL cortex and configural memory is a novel observation in the human brain but strongly converges with observations from amnesia patients. In addition, the dissociation between processing in anterior (entorhinal/perirhinal) and posterior (parahippocampal) MTL cortex conveys the need to consider these regions separately in theories of MTL function in memory. Together these findings, therefore, contribute to the view that different MTL structures make distinct contributions to human memory.

Funding

National Institute of Mental Health (MH63576 to A.R.P. and MH59940 to J.D.E.G.).

Supplementary Material

Supplementary results can be found at: http://www.cercor.oxfordjournals.org/.

Notes

We thank Daphna Shohamy and the anonymous reviewers for their insightful commentary on earlier versions of this manuscript, Joanna Salidis for assistance with task design and programming, and Sirisha Narayana for assistance with data analysis. *Conflict of Interest*: None declared.

Address correspondence to email: apreston@mail.clm.utexas.edu.

References

Amaral DE, Insausti R. 1990. Hippocampal formation. In: Paxinos G, editor. The human nervous system. San Diego (CA): Academic Press. p. 711–755.

Barense MD, Bussey TJ, Lee AC, Rogers TT, Davies RR, Saksida LM, Murray EA, Graham KS. 2005. Functional specialization in the human medial temporal lobe. J Neurosci. 25:10239–10246.

Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD. 1998. Making memories: brain activity that predicts how well visual experience will be remembered. Science. 281:1185–1187.

Brown MW, Aggleton JP. 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci. 2:51–61.

Brown MW, Xiang JZ. 1998. Recognition memory: neuronal substrates of the judgement of prior occurrence. Prog Neurobiol. 55:149–189.

Bunge SA, Burrows B, Wagner AD. 2004. Prefrontal and hippocampal contributions to visual associative recognition: interactions between cognitive control and episodic retrieval. Brain Cogn. 56:141–152.

Bunsey M, Eichenbaum H. 1996. Conservation of hippocampal memory function in rats and humans. Nature. 379:255–257.

Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL. 2001. Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci USA. 98:4805–4810.

Cansino S, Maquet P, Dolan RJ, Rugg MD. 2002. Brain activity underlying encoding and retrieval of source memory. Cereb Cortex. 12:1048–1056.

Chun MM, Jiang Y. 1998. Contextual cueing: implicit learning and memory of visual context guides spatial attention. Cogn Psychol. 36:28–71.

Chun MM, Jiang Y. 2003. Implicit, long-term spatial contextual memory. J Exp Psychol Learn Mem Cogn. 29:224–234.

Chun MM, Phelps EA. 1999. Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. Nat Neurosci. 2:844–847.

Cocosco CA, Kollokian V, Kwan RKS, Evans AC. 1997. Online interface to a 3D MRI simulated brain database. Neuroimage. 5:425.

Cohen J, MacWhinney B, Flatt M, Provost J. 1993. Psyscope: an interactive graphical system for designing and controlling experiments in the Psychology laboratory using Macintosh computers. Behav Res Methods Instrum Comput. 25:257–271.

Cohen NJ, Poldrack RA, Eichenbaum H. 1997. Memory for items and memory for relations in the procedural/declarative memory framework. Memory. 5:131–178.

Cohen NJ, Squire LR. 1980. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science. 210:207–210.

Daselaar SM, Fleck MS, Cabeza R. 2006. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J Neurophysiol. 96:1902–1911.

Daselaar SM, Fleck MS, Prince SE, Cabeza R. 2006. The medial temporal lobe distinguishes old from new independently of consciousness. J Neurosci. 26:5835–5839.

Davachi L, Mitchell J, Wagner AD. 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc Natl Acad Sci USA. 100:2157–2162.

Davachi L, Wagner AD. 2002. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol. 88:982–990.
Dusek JA, Eichenbaum H. 1997. The hippocampus and memory for orderly stimulus relations. Proc Natl Acad Sci USA. 94:7109–7114.
Eichenbaum H. 1994. The hippocampal system and declarative memory in humans and animals: experimental analysis and historical origins. In: Schacter DL, Tulving E, editors. Memory systems 1994. Cambridge (MA): The MIT Press. p. 147–201.
Eichenbaum H, Cohen NJ. 2001. From conditioning to conscious recollection: memory systems of the brain. New York: Oxford University Press.
Eichenbaum H, Schoenbaum G, Young B, Bunsey M. 1996. Functional organization of the hippocampal memory system. Proc Natl Acad Sci USA. 93:13500–13507.
Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA. 2000. Remembering episodes: a selective role for the hippocampus during retrieval. Nat Neurosci. 3:1149–1152.
Eliassen JC, Souza T, Sanes JN. 2001. Human brain activation accompanying explicitly directed movement sequence learning. Exp Brain Res. 141:269–280.
Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp. 2:189–210.
Friston KJ, Jezzard P, Turner R. 1994. Analysis of functional MRI time-series. Hum Brain Mapp. 1:153–171.
Gabrieli JD. 1998. Cognitive neuroscience of human memory. Annu Rev Psychol. 49:87–115.
Geng JJ, Behrmann M. 2005. Spatial probability as an attentional cue in visual search. Percept Psychophys. 67:1252–1268.
Glover GH, Lai S. 1998. Self-navigated spiral fMRI: interleaved versus single-shot. Magn Reson Med. 39:361–368.
Gomez-Beldarrain M, Garcia-Monco JC, Rubio B, Pascual-Leone A. 1998. Effect of focal cerebellar lesions on procedural learning in the serial reaction time task. Exp Brain Res. 120:25–30.
Gomez-Beldarrain M, Grafman J, Pascual-Leone A, Garcia-Monco JC. 1999. Procedural learning is impaired in patients with prefrontal lesions. Neurology. 52:1853–1860.
Gonsalves BD, Kahn I, Curran T, Norman KA, Wagner AD. 2005. Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. Neuron. 47:751–761.
Graf P, Schacter DL. 1985. Implicit and explicit memory for new associations in normal and amnesic subjects. J Exp Psychol Learn Mem Cogn. 11:501–518.
Greene AJ, Gross WL, Elsinger CL, Rao SM. 2006. An fMRI analysis of the human hippocampus: inference, context, and task awareness. J Cogn Neurosci. 18:1156–1173.
Heckers S, Zalesak M, Weiss AP, Ditman T, Titone D. 2004. Hippocampal activation during transitive inference in humans. Hippocampus. 14:153–162.
Henson RNA, Rugg MD. 2003. Neural response suppression, haemodynamic repetition effects, and behavioral priming. Neuropsychologia. 41:263–270.
Holmes AP, Friston KJ. 1998. Generalizability, random effects, and population inference. Neuroimage. 7:S754.
Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkanen A. 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol. 19:659–671.
Jiang Y, Wagner LC. 2004. What is learned in spatial contextual cuing—configuration or individual locations? Percept Psychophys. 66:454–463.
Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000. Prefrontal-temporal circuitry for novelty encoding and subsequent memory. J Neurosci. 20:6173–6180.
Kirwan CB, Stark CE. 2004. Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. Hippocampus. 14:919–930.
Lee AC, Bussey TJ, Murray EA, Saksida LM, Epstein RA, Kapur N, Hodges JR, Graham KS. 2005. Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. Neuropsychologia. 43:1–11.
Manns JR, Squire LR. 2001. Perceptual learning, awareness, and the hippocampus. Hippocampus. 11:776–782.
Marr D. 1971. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci. 262:23–81.
McClelland JL, McNaughton BL, O'Reilly RC. 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol Rev. 102:419–457.
Miller J. 1988. Components of the location probability effect in visual search tasks. J Exp Psychol Hum Percept Perform. 14:453–471.
Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S. 2003. Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. Neuron. 38:305–315.
Norman KA, O'Reilly RC. 2003. Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. Psychol Rev. 110:611–646.
Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE. 1997. Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. Neuroimage. 6:156–167.
O'Reilly RC, Rudy JW. 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol Rev. 108:311–345.
Otten LJ, Henson RN, Rugg MD. 2001. Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain. 124: 399–412.
Poldrack RA, Clark J, Pare-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C, Gluck MA. 2001. Interactive memory systems in the human brain. Nature. 414:546–550.
Preston AR, Shrager Y, Dudukovic NM, Gabrieli JD. 2004. Hippocampal contribution to the novel use of relational information in declarative memory. Hippocampus. 14:148–152.
Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M. 2003. Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia. 42:2–13.
Reber PJ, Knowlton BJ, Squire LR. 1996. Dissociable properties of memory systems: differences in the flexibility of declarative and nondeclarative knowledge. Behav Neurosci. 110:861–871.
Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. 1996. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci. 16:5233–5255.
Rose M, Haider H, Weiller C, Buchel C. 2002. The role of medial temporal lobe structures in implicit learning: an event-related fMRI study. Neuron. 36:1221–1231.
Rutishauser U, Mamelak AN, Schuman EM. 2006. Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. Neuron. 49:805–813.
Schacter DL, Wagner AD. 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus. 9:7–24.
Schnyer DM, Dobbins IG, Nicholls L, Schacter DL, Verfaellie M. 2006. Rapid response learning in amnesia: delineating associative learning components in repetition priming. Neuropsychologia. 44:140–149.
Seger CA, Poldrack RA, Prabhakaran V, Zhao M, Glover GH, Gabrieli JD. 2000. Hemispheric asymmetries and individual differences in visual concept learning as measured by functional MRI. Neuropsychologia. 38:1316–1324.
Squire LR. 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev. 99:195–231.
Squire LR, Stark CE, Clark RE. 2004. The medial temporal lobe. Annu Rev Neurosci. 27:279–306.
Stark CE, Squire LR. 2003. Hippocampal damage equally impairs memory for single items and memory for conjunctions. Hippocampus. 13: 281–292.
Stark CEL, Bayley PJ, Squire LR. 2002. Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. Learn Mem. 9:238–242.
Strange BA, Otten LJ, Josephs O, Rugg MD, Dolan RJ. 2002. Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. J Neurosci. 22:523–528.

Tulving E. 1983. Elements of episodic memory. London: Oxford University Press.
Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science. 281:1188–1191.
Weis S, Klaver P, Reul J, Elger CE, Fernandez G. 2004. Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. Cereb Cortex. 14:256–267.
Weis S, Specht K, Klaver P, Tendolkar I, Willmes K, Ruhlmann J, Elger CE, Fernandez G. 2004. Process dissociation between contextual retrieval and item recognition. Neuroreport. 15:2729–2733.
Zola-Morgan S, Squire LR, Amaral DG. 1986. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 9:2950–2967.