Behavioral/Cognitive

Hippocampal Binding of Novel Information with Dominant Memory Traces Can Support Both Memory Stability and Change

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Memory stability and change are considered opposite outcomes. We tested the counterintuitive notion that both depend on one process: hippocampal binding of memory features to associatively novel information, or associative novelty binding (ANB). Building on the idea that dominant memory features, or "traces," are most susceptible to modification, we hypothesized that ANB would selectively involve dominant traces. Therefore, memory stability versus change should depend on whether the currently dominant trace is old versus updated; in either case, novel information will be bound with it, causing either maintenance (when old) or change (when updated). People in our experiment studied objects at locations within scenes (contexts). During reactivation in a new context, subjects moved studied objects to new locations either via active location recall or by passively dragging objects to predetermined locations. After active reactivation, the new object location became dominant in memory, whereas after passive reactivation, the old object location maintained dominance. In both cases, hippocampal ANB bound the currently dominant object-location memory with a context with which it was not paired previously (i.e., associatively novel). Stability occurred in the passive condition when ANB united the dominant original location trace with an associatively novel newer context. Change occurred in the active condition when ANB united the dominant updated object location with an associatively novel and older context. Hippocampal ANB of the currently dominant trace with associatively novel contextual information thus provides a single mechanism to support memory stability and change, with shifts in trace dominance during reactivation dictating the outcome.

Key words: **memory; reactivation; reconsolidation; relational binding; retrieval; trace dominance**

Introduction

Memory can endure for decades yet also can change to maintain relevance (Dudai and Eisenberg, 2004; Iordanova et al., 2011; Dudai, 2012). Although stability and change are considered opposite outcomes caused by distinct neural processes, this idea has not received direct support. Here we test the counterintuitive hypothesis that one hippocampal binding mechanism for flexible memory updating supports both stability and change.

Investigations of memory stability and change have emphasized the role of memory retrieval. "Testing effects" occur when retrieval of information during a memory test increases the likelihood that the same information will endure more than does simply restudying the information (Hogan and Kintsch, 1971; Runquist, 1983; Carrier and Pashler, 1992; Karpicke and Roediger, 2008). Retrieval could thus promote memory stability. In contrast, various "reconsolidation" phenomena suggest that retrieval might provide a window of opportunity for change. At specific times after learning, reinstatement of the learning context followed by a blockade of new learning can disrupt the original memory but only when it is reactivated via a contextual reminder cue (Hupbach et al., 2007, 2008). Retrieval could thus bridge the original memory to information encountered in the current context, thereby updating old representations with newly relevant information (Iordanova et al., 2011; Dudai, 2012).

Whether retrieval promotes stability versus change could depend on the relative dominance of the various component parts (traces) of a multidimensional memory. During retrieval, several memory traces may compete, including traces from initial learning and traces from subsequent retrieval events (Lewis, 1979; Berman et al., 2003; Dudai and Eisenberg, 2004). Of these competing traces, the strongest tends to control behavior and, interestingly, may be most susceptible to modification. Indeed, dominant traces are most influenced by consolidation blockers (Eisenberg et al., 2003), suggesting that they change more than nondominant traces. Hippocampal-dependent binding during retrieval could thus integrate the dominant trace with current contextual information (Honey et al., 1998). Associative novelty binding (ANB) occurring between traces and contexts that have

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not been presented together previously during retrieval could therefore support stability (when the original dominant trace is bound with novel contextual information) and also change (when new dominant traces are bound with original contextual information). Although the hippocampus has been implicated in associative novelty detection (Kumaran and Maguire, 2007), here, we test whether it selectively binds associatively novel information and whether ANB is selective for currently dominant traces.

We tested the idea that ANB promotes either memory stability or change depending on trace dominance. A novel paradigm allowed us to manipulate object-location trace dominance and to isolate neural activity related to binding the dominant trace to new contextual information. We manipulated trace dominance as follows: object-location dominance shifted after active location recall, whereby the recalled (updated) location was later remembered in favor of the original location. In contrast, no dominance shift occurred after passively moving the object to a predetermined updated location, such the original location was later remembered in favor of the updated location. We identified brain activity related to eye-movement measures of trace dominance and to binding of the dominant trace to a novel context to test the hypothesis that hippocampal ANB promotes stability (binding original object-location traces to novel contexts) versus change (binding updated, dominance-shifted, object-location traces to familiar contexts).

Materials and Methods

Overview of study design and rationale. To manipulate and measure trace dominance as well as ANB, we used an object-location memory task with three phases performed by subjects during concurrent fMRI and eye tracking. In this paradigm, each "memory" comprised two features: an object location and a context (background scene). Each object had two associated locations: an older location (originally studied) and a newer (updated) location. Thus, we were able to manipulate the dominance of the object-location trace in memory by making either the older object location or the newer object location dominant (as described below). Furthermore, the two locations for each object were initially encountered in separate contexts: the older object location was encountered in one scene, whereas the updated object location was encountered in a second scene. We were thus able to examine ANB by later testing memory of the object locations in either the first (older) scene or the second (newer) scene. The primary logic of our experiment was to determine whether brain activity related to ANB was specific to when dominant traces (regardless of whether they were older or newer) were paired with associatively novel contexts (i.e., had not been paired together previously). Furthermore, we sought to determine whether this ANB-related brain activity predicted memory stability versus change. That is, when dominant older object location traces were paired with newer contexts, ANB should predict the extent to which the older object location maintains its dominance despite the newer context (stability). In contrast, when dominant newer object location traces were paired with older contexts, ANB should predict the extent to which the newer object location maintains its dominance, thus reflecting a change in the memory for the pairing of the older context with the newer object location. We reasoned that this ANB-related activity would correspond to memory stability versus memory change to the extent to which it was related to the expression of memory for the original object location in a newer context (stability) versus the expression of memory for the newer object location in an older context (change).

Participants. Data were collected from 20 people (11 women; aged 19–30 years, mean of 26 years). All were right-handed, free of history of neurological impairment, and currently not taking any psychoactive drugs. Data from three participants were excluded because of failure of eye-movement calibration during MRI scanning, leaving a total of 17 participants for the reported analyses. Written informed consent was obtained from all subjects before participation in accordance with the Northwestern University Institutional Review Board. Subjects were compensated for their participation. All subjects but one contributed trials from two Active and two Passive blocks to the behavioral, eye movement, and fMRI analysis, with data from only one Active block and two Passive blocks in one subject because of a computer failure.

Stimuli. A set of 168 images of real-life objects was used (Moreno-Martínez and Montoro, 2012). Object dimensions were 3.09 × 1.86 cm. Eight photographs depicting real-life scenes were used as the background context images (Yue et al., 2007). The screen resolution was 1280 × 1024 pixels, which occupied 26.25 × 21 cm on the MRI projector screen. The refresh rate was 60 Hz. Each object was presented with a red dot marking its center, which could be anywhere such that the whole object was visible on the background. Thus, objects could appear anywhere within the central 24.75 × 19.60 cm area of the screen.

Procedure. Each block of the task comprised three phases, Study, Refresh, and Recognition (Fig. 1*A*), each separated by a 5 min distractor task involving visual discrimination of fractal images and simultaneous one-back working memory performance. There were four blocks, two with an Active Refresh phase and two with a Passive Refresh phase. Each block included a novel background image for $Context_1$ and $Context_2$. During Study, participants viewed 42 objects presented at unique locations on the screen ($Location_1$) in $Context_1$. The $Context_1$ scene background remained on the screen throughout the Study phase as objects were individually presented at randomized locations for 3000 ms each. A 1000 ms fixation cross preceded the presentation of each object.

A different scene was shown during Refresh ($Context_2$). A fixation cross superimposed on a gray background preceded each refresh trial. The length of the fixation trial was jittered (0–14 s) to maximize BOLD signal estimates (see below). Each Refresh trial was 5000 ms. A centrally presented object from the preceding Study phase appeared on the screen, and participants were prompted to move the object using a trackball mouse. During Active Refresh, participants dragged the object from the center of the screen to its recalled location and then pressed a button. The object remained in the selected location until the end of the trial. The precise placement of $Location_2$ (the recalled location) always diverged from $Location_1$ (the location at Study) to some extent (mean ± SE, 9.01 ± 0.37 cm). Divergence distances (i.e., placement error) for each object were used to generate the location of objects during Passive Refresh (described below).

During Passive Refresh, participants were prompted to move each object from the center of the screen to a predetermined location. The centrally presented object was accompanied by the presentation of a yellow target box in a predetermined location, and participants moved the object to the box and pressed a button. Placement within 0.5 cm of the center point of the yellow box was required for the response to be accepted. After the response was accepted, the object moved to the center of the yellow box and remained in that position until the end of the trial. Participants were told that the yellow box would be located in $Location_1$ for some of the trials and located in a novel location on other trials, analogous to ranging levels of recall accuracy in the Active condition.

A matching procedure was used such that the divergence distances (distance between $Location_2$ and $Location_1$) were approximately equivalent for Active and Passive Refresh. The divergence distance of the yellow box for each Passive trial was thus matched to the divergence distance from a randomly selected trial from the Active condition, yielding approximately the same mean divergence (mean ± SE, 8.93 ± 0.34 cm). The mean displacement distances for Active and Passive Refresh differed slightly as a result of rounding error but not significantly ($t_{(16)} = 1.39$, NS). This matching scheme dictated that the first Active Refresh block always precede its matching Passive Refresh block. The first block was always with Active Refresh, and the last block was always with Passive Refresh. The order (Active or Passive) of the two intermediate blocks was counterbalanced across participants. Objects and scenes were randomly assigned to the Active or Passive Refresh condition.

For the Recognition test, half of the objects were tested using the $Context_1$ scene, and the other half were tested using the $Context_2$ scene. Objects were pseudorandomly assigned to the $Context_1$ or $Context_2$ Recognition conditions based on displacement distances from the Refresh

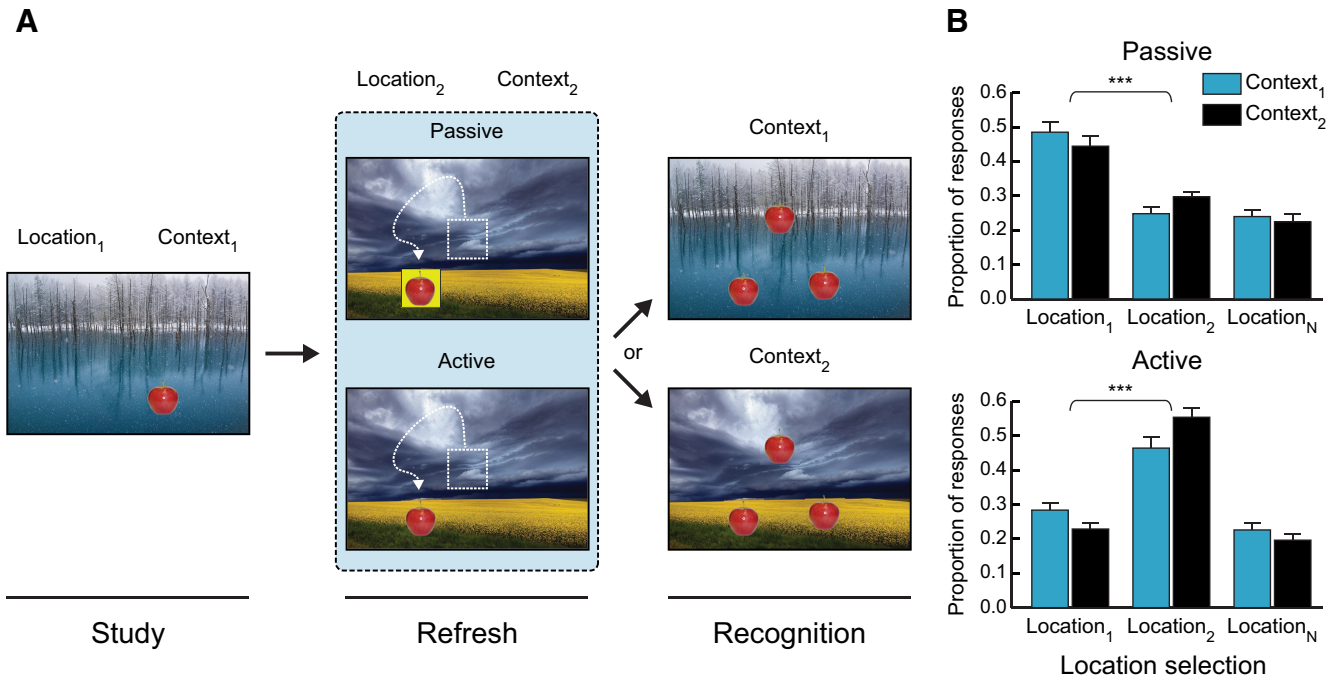

Figure 1. Experimental manipulation of memory maintenance versus change. ***A***, Object locations were first studied on a novel scene background ($Context_1$). Then, either Passive or Active Refresh occurred using a new scene background ($Context_2$). In Passive Refresh, subjects dragged the object to a yellow box in a predetermined location. In Active Refresh, subjects attempted to recall the location of the object by dragging the object to that location. During Recognition, subjects selected the location of the object from among three choices: the original study location ($Location_1$), the Refresh location ($Location_2$), and an equidistant new location ($Location_N$). Recognition was tested in either $Context_1$ or $Context_2$. ***B***, Recognition responses are shown for Passive and Active Refresh and for both Recognition contexts. Memory of $Location_1$ was maintained in the Passive Refresh condition, whereas memory dominance shifted to $Location_2$ in the Active condition. Note that each of the four experimental blocks included either Active or Passive Refresh. Different objects, locations, and background scenes were used in each block. $^{***}p < 0.001$. Error bars represent SE.

phase, such that the mean distance between $Location_1$ and $Location_2$ was matched across test context conditions. The lure location ($Location_N$) was determined for each object by rotating $Location_2$ about the axis of $Location_1$ by 60° or 240°. If an equidistant lure location could not be identified because of screen-size constraints, the rotation angle was systematically reduced or increased until the object could be fully visible on the screen in $Location_N$. To avoid visual overlap of the images, a second lure location was randomly selected to replace $Location_2$ for those objects in the Active Refresh condition that had been recalled within 1.86 cm of $Location_1$ during the Refresh phase. These trials were excluded from all analyses (mean ± SE, 8.71 ± 1.33 trials per subject, ranging from 0 to 21 trials). A fixation cross superimposed on a gray background preceded each Recognition trial. The length of the fixation trial was jittered (0–24 s). After a fixation trial, a background image ($Context_1$ or $Context_2$) appeared on the screen. At the same time, an object appeared in three locations: $Location_1$, $Location_2$, and $Location_N$. To ensure rapid visibility, the object flashed once (100 ms on, 100 ms off) while the background image remained constantly visible. Then, the object remained displayed constantly in the three locations for an additional 4800 ms. During this 5000 ms period, eye movements were recorded. The objects then disappeared from the screen and were immediately replaced by a number label (1, 2, or 3) in each of the locations for 2000 ms. Participants were instructed to press the number on a keypad that corresponded to the location in which they studied the object. Locations were always numbered in ascending order from left to right on the screen, and the numbers did not systematically correspond to correct answers.

fMRI methods. We measured fMRI BOLD signal changes during Refresh and Recognition using a Siemens 3T Trio scanner. fMRI data were not obtained during Study. Eye movements were recorded concurrently during Recognition. BOLD fMRI was conducted using standard whole-brain parameters (TR, 2000 ms; TE, 20 ms; FOV, 220 mm; voxel size, 1.5 × 1.5 × 3 mm; 195 volumes collected during each Refresh phase, 276 volumes collected during each Recognition phase). Structural MRI was obtained after the task to provide anatomical localization (MP-RAGE T_1-weighted scans; voxel size, 1 mm^3; FOV, 256; 176 sagittal slices). Responses were made with the right hand using an MRI-compatible button box (for Recognition) and an MRI-compatible trackball mouse (for Refresh). The timing between events was jittered to optimize the separation of estimated signal for each condition with an event-related design. The mean ISI for Recognition was 12.43 s, ranging from 7 to 31 s, and the mean ISI for Refresh was 9 s, ranging from 5 to 19 s.

fMRI data were analyzed using AFNI (Cox, 1996). Preprocessing steps included motion correction, correction of slice-timing discrepancies, coregistration of structural and functional images, transformation to stereotactic space (MNI), removal of linear signal drift, and spatial smoothing of functional data with a 4 mm FWHM Gaussian kernel. Functional images were aligned to the structural image, and then both were converted to stereotactic space using a standard template (Rex et al., 2003). Eye-movement measures of memory obtained during the Recognition phase were used to segregate trials into multiple conditions, and parameter estimates corresponding to these conditions were obtained for each subject using a deconvolution approach within a general linear model (as in standard event-related fMRI designs). Eye-movement measures were used to create conditions as follows: successful versus unsuccessful location-memory maintenance conditions and successful versus unsuccessful location-memory dominance conditions (as described below) were created and then further divided based on Recognition context ($Context_1$, $Context_2$), and Refresh condition (Active, Passive). Nuisance variables included T_0 and T_1* components of the MR signal and six-parameter movement estimates. Trials were modeled using a regressor generated by convolving a boxcar function corresponding to 5 s trial periods for Refresh or 7 s trial periods for Recognition with a canonical hemodynamic response function. Regions exhibiting significant activity at the group level were identified via random-effects analysis with a combined voxelwise and spatial extent threshold method incorporating Monte Carlo simulation (Forman et al., 1995) and mixed-effects multilevel analysis (Chen et al., 2012). The voxelwise threshold was set to $p < 0.001$, and the spatial-extent threshold for whole-brain analyses was identified as 79 contiguous suprathreshold voxels to obtain a combined corrected threshold of $p < 0.01$ (identified for the most conservative level

for any contrast and applied to all contrasts). A threshold of 15 voxels was used for planned assessments of activity within medial temporal lobe (MTL) structures (hippocampus, parahippocampal gyrus, and perirhinal and entorhinal cortices).

Eye-tracking methods. Eye movements were recorded at 500 Hz during recognition trials using an Eyelink 1000 remote tracking system (SR Research) that was focused on the right eye via the mirror that subjects used to view the projection screen in the MRI scanner. The continuous eye-movement records were transformed into a time series of fixations, saccades, and blinks. Motion (0.15°), velocity (30°/s), and acceleration (8000°/s^2) thresholds were used to identify saccades. Events in which the pupil size was very small were classified as blinks. Otherwise, eye-movement events falling below the saccade detection thresholds were categorized as fixation events. The average eye position was calculated over the duration of each fixation event. The duration and time course of fixations in regions of interest (ROIs) were analyzed using custom scripts in MATLAB (MathWorks). ROIs were circles that encompassed the three locations of each object during Recognition ($Location_1$, $Location_2$, and $Location_N$). By default, the radius of the ROI was equivalent to the diagonal of the object (3.09 cm). However, on trials in which objects were located close together such that the default ROIs would overlap, the radius of the ROI was reduced to equal half the distance between any two locations. On average, the ROI radius was 2.70 ± 0.04 cm (mean ± SE).

Eye movements were recorded during the first 5 s of each Recognition trial, when the object was displayed on the screen in three locations. We analyzed eye movements for each Recognition trial by first summing the total time spent fixating within the three ROIs. We then divided the total viewing time directed to each individual ROI by the total ROI viewing time to obtain a location-based proportion of viewing time measurement for each trial. Trials with <20% total viewing time directed to the three ROIs were excluded from all eye-movement-related analysis (mean of 4.38, range of 0–11 trials in the Active condition; and mean of 7.94, range 0 of 21 trials in the Passive condition).

Eye movements and button-press responses were assessed using repeated measures (RM)-ANOVA. A Bonferroni-corrected p value was set to $p = 0.0083$ based on the number of planned comparisons we conducted on the recognition responses and $p = 0.0056$ based on the number of planned comparisons we conducted on the eye-movement data. Huyn–Feldt correction was used for violations of sphericity, denoted HF in text when applicable.

Results

Manipulating trace dominance during memory refresh

Based on previous evidence that retrieval can promote shifts in object-location trace dominance (Bridge and Paller, 2012), we used two conditions that differed in retrieval promotion to manipulate trace dominance. Subjects ($n = 17$) first studied objects at particular locations in $Context_1$. After study, subjects attempted to recall object locations in the Active Refresh condition or merely dragged objects to predetermined locations in the Passive Refresh condition (Fig. 1*A*). We predicted that object-location dominance would shift selectively in the Active Refresh condition, such that subjects would later remember the location from the Active Refresh event ($Location_2$) as opposed to the original studied location ($Location_1$). In contrast, we predicted that no dominance shift would occur for Passive Refresh, such that subjects would later remember $Location_1$ rather than $Location_2$. Critically, Refresh occurred in a new context relative to original study ($Context_2$), and subsequent testing in the Recognition portion of the experiment occurred in either $Context_1$ or $Context_2$ (Fig. 1*A*). These manipulations allowed us to isolate dominance shift from the effects of context on recognition memory and from the effects of recency.

As predicted, memory outcomes during Recognition differed significantly after Active versus Passive Refresh (Fig. 1*B*). We examined the proportion of responses as a function of Refresh condition (Active, Passive), the location that subjects selected during the Recognition test ($Location_1$, $Location_2$, $Location_N$), and context during the Recognition test ($Context_1$, $Context_2$). A crossover interaction of Refresh condition with location selection ($F_{(1.61,25.80)} = 40.60, p < 0.001_{HF}$) resulted because $Location_2$ was selected more often after Active Refresh than Passive Refresh ($t_{(16)} = 7.11$, $p < 0.001$), whereas $Location_1$ was selected more often after Passive Refresh than Active Refresh ($t_{(16)} = 6.42$, $p < 0.001$). This finding indicates that a dominance shift occurred for Active Refresh, but the dominance of the original location was maintained for Passive Refresh.

These location maintenance and dominance-shift effects occurred regardless of the match between context during Recognition and the previously encountered context. However, recognition context interacted with location selection, in that locations were more likely to be recognized in the context in which they had previously been encountered rather than the associatively novel context ($F_{(2,32)} = 10.44, p < 0.001_{HF}$). Whereas $Location_1$ was selected more often in $Context_1$ than $Context_2$ ($t_{(16)} = 3.12$, $p < 0.007$), $Location_2$ was selected more often in $Context_2$ than $Context_1$ ($t_{(16)} = 4.18, p < 0.001$). Critically, these effects of context were eclipsed by the Active Refresh dominance shift and the Passive Refresh dominance maintenance effects. For Active Refresh, $Location_2$ was selected more often than $Location_1$ in $Context_1$ ($t_{(16)} = 3.44$, $p < 0.005$) and $Context_2$ ($t_{(16)} = 7.60$, $p < 0.001$), whereas for Passive Refresh, $Location_1$ was selected more often than $Location_2$ in $Context_1$ ($t_{(16)} = 5.72, p < 0.001$) and $Context_2$ ($t_{(16)} = 3.44$, $p < 0.005$).

Therefore, Active Refresh shifted object-location trace dominance across contexts, whereas Passive Refresh was associated with maintenance of trace dominance across contexts (i.e., no shift during Refresh). This Active/Passive distinction in dominance-shift outcome was not caused by nonspecific factors such as temporal proximity of viewing $Location_2$ during Active Refresh to Recognition or to context effects, because these factors were matched for the Active and Passive Refresh conditions. Furthermore, we explicitly matched distances between $Location_2$ and $Location_1$ for Active and Passive conditions (see Materials and Methods). The dominance-shift effect thus occurred selectively and robustly for the Active Refresh condition, with 16 of 17 subjects (94%) demonstrating Active Refresh dominance shift for both contexts, and 15 of 17 subjects (88%) demonstrating Passive Refresh dominance maintenance for both contexts. Finally, the Active Refresh dominance shift was not merely a product of poor retrieval of $Location_1$, because the dominance shift was equally likely when object-location recall was relatively successful versus when it was relatively unsuccessful (see analysis at the end of Results).

Eye movements also indicate dominance maintenance and dominance shift

We examined eye movements during Recognition to determine how they corresponded to overt response selections. Figure 2*A* shows example eye movements for one trial. We subjected the overall proportion of viewing time to RM-ANOVA with Refresh condition (Active, Passive) and location option ($Location_1$, $Location_2$, $Location_N$) as factors (Fig. 2*B*). Consistent with the Recognition response analysis, we observed a main effect of location ($F_{(1.78,28.44)} = 11.36, p < 0.001_{HF}$). However, this main effect was qualified by an interaction of Refresh condition and location ($F_{(2.00,32.00)} = 17.66, p < 0.001_{HF}$). Whereas more time was spent viewing $Location_1$ in the Passive versus in the Active condition ($t_{(16)} = 4.08, p < 0.001$), more time was spent viewing $Location_2$ in the Active versus in the Passive condition ($t_{(16)} = 5.35$, $p <$

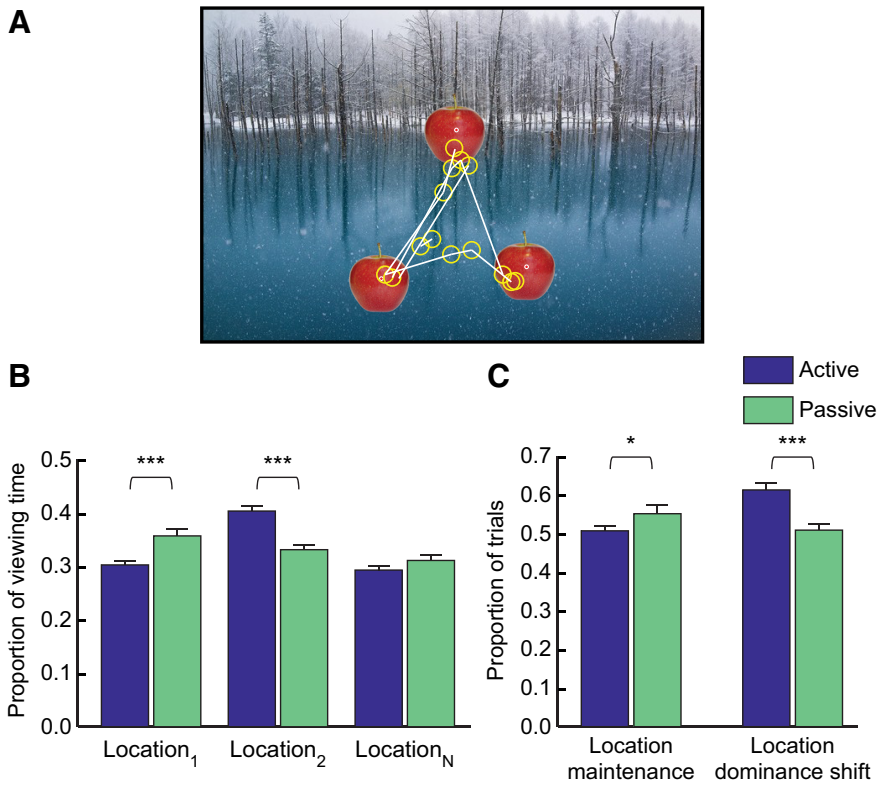

Figure 2. Eye movements during Recognition. ***A***, Example trial from one participant. Yellow circles depict fixations; white lines depict saccades. ***B***, Proportion of viewing time for each object location option during Recognition is plotted as function of Refresh condition, regardless of response selection. More time was spent viewing $Location_1$ after Passive rather than Active Refresh, whereas more time was spent viewing $Location_2$ after Active rather than Passive Refresh. ***C***, Proportion of trials allocated to successful location-memory maintenance and successful location-memory dominance conditions for fMRI analysis. Successful maintenance was defined as trials in which more time was spent viewing $Location_1$ versus $Location_N$ during Recognition, and successful dominance shift trials were defined as those trials in which more time was spent viewing $Location_2$ versus $Location_N$ during Recognition. More trials in the Passive versus the Active condition were allocated to the successful location-memory maintenance condition, whereas more trials in the Active versus Passive condition were allocated to the successful location-memory dominance shift condition. $*p < 0.05$, $***p < 0.001$. Error bars represent SE.

0.001). Within the Active condition, more time was spent viewing $Location_2$ relative to both $Location_1$ ($t_{(16)} = 7.14$, $p < 0.001$) and $Location_N$ ($t_{(16)} = 6.76$, $p < 0.001$). In the Passive condition, more viewing time tended to be allocated to $Location_1$ relative to the other conditions; however, these differences were not significant ($Location_1$ vs $Location_2$: $t_{(16)} = 1.27$, NS; $Location_1$ vs $Location_N$: $t_{(16)} = 1.87$, $p < 0.08$). These results are consistent with the Recognition response analysis, supporting our use of eye movements to categorize trials into conditions for fMRI analysis (described in detail below).

ANB by hippocampus

Having identified the dominant object-location traces during different portions of the experiment, we were able to test hypotheses regarding binding of the dominant trace to context information that was novel relative to the dominant trace (i.e., context information not presented previously with the currently dominant trace) or ANB. As shown in Figure 3, we predicted that the dominant original location ($Location_1$) would be bound with $Context_2$ during Passive Refresh. Furthermore, we reasoned that the magnitude of this binding would predict the later tendency to recognize $Location_1$ when given $Context_2$ during Recognition. That is, to the extent that activity during Passive Refresh reflects binding and not mere detection of associative novelty, it would selectively predict the later tendency to recognize $Location_1$ in $Context_2$, because $Location_1$–$Context_1$ was already bound during the initial Study event. This outcome can be distinguished from activity that would result if mere location-context novelty detection occurred without binding, in which case activity would not predict later Recognition performance. The predicted outcome is also distinct from what would be expected had $Location_1$ not been reactivated during Refresh, in which case no binding with $Context_2$ would occur and no selective neural activity would be identified. Selectivity of neural activity as hypothesized in Figure 3 would therefore indicate the ANB mechanism we propose.

In contrast to these predictions for Passive Refresh, we reasoned that ANB would not occur during Active Refresh. Instead, dominance shift occurred during Active Refresh, such that the new location ($Location_2$) became directly associated with $Context_2$ (neural correlates of dominance shift are reported below). Therefore, the critical binding between the dominant trace and the novel context would occur during the subsequent Recognition test in $Context_1$ rather than during Refresh. Neural activity reflecting ANB during the Recognition test would be selective for $Context_1$, given that this context is novel relative to the dominant trace ($Location_2$), whereas $Context_2$ was already presented with $Location_2$ during Active Refresh. In contrast, location-context novelty detection without binding would produce similar activity for Active and Passive conditions during Recognition, because $Location_2$ was not paired previously with $Context_1$ for either Active or Passive conditions.

Finally, we reasoned that evidence for ANB would be obtained if the same neural activity were identified in both of the aforementioned contrasts (Passive Refresh predicting $Location_1$ selection in $Context_2$ and Active Recognition of $Location_2$ only when tested in $Context_1$; Fig. 3). That is, the pattern of activity would reflect the hypothesized binding mechanism to the extent that it occurs only when the current dominant object-location trace is novel with respect to the current context and is insensitive to any and all factors that vary between the Active and Passive conditions, to any differences between Refresh or Recognition, and to the processing responsible for general associative learning and retrieval that occurs in several phases of the experiment. Based on the considerations reviewed above, we predicted that the selective ANB effects thus hypothesized would include primarily involvement of hippocampus.

We used eye movements rather than recognition button-push responses to categorize trials for fMRI analyses for three reasons. First, recognition selections provide only discrete measurements of memory and do not capture the relative amount of location-memory maintenance versus location-memory dominance shift that occurred for each trial (i.e., maintenance vs dominance shift could have occurred to some extent on all trials, even when a different location, such as $Location_N$, was selected). In contrast,

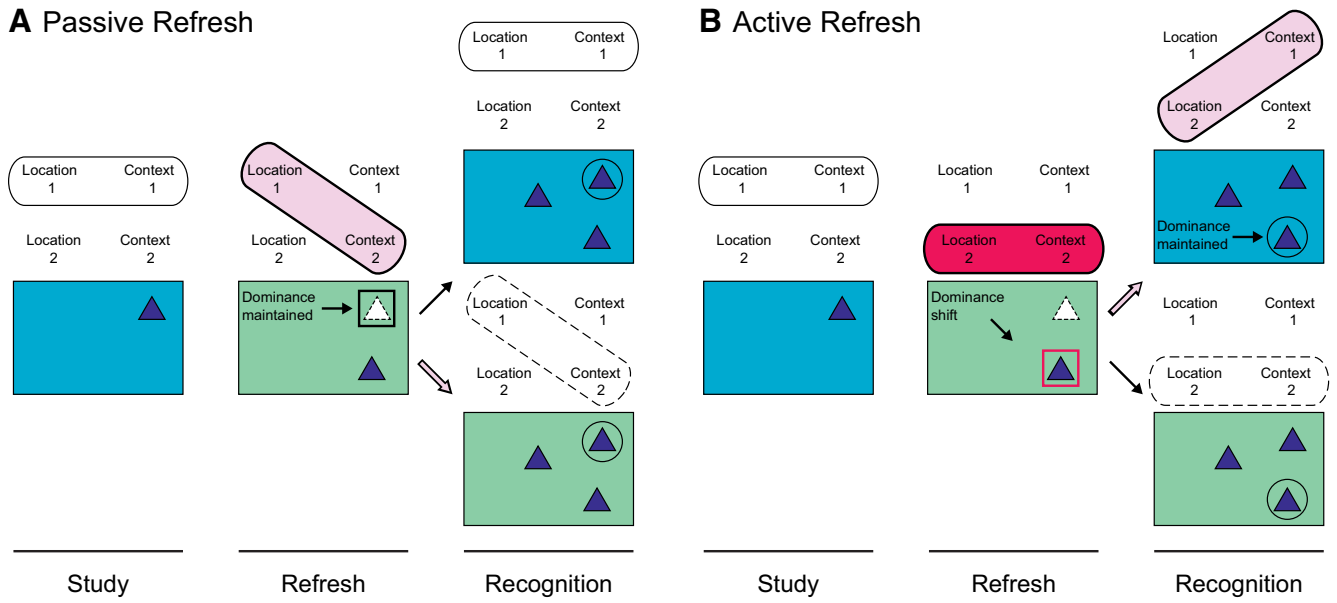

Figure 3. Hypothesized occurrence of fMRI activity related to ANB. Navy triangles represent locations where an example object was displayed in each phase; the white triangle represents the original location of the object, which was not actually displayed during the Refresh phase. The blue background represents $Context_1$, and the green background represents $Context_2$. ***A***, We predicted that ANB (depicted by the pink diagonal bar) would occur during Passive Refresh because $Context_2$ was associatively novel with respect to the dominant location memory ($Location_1$), which had been tied previously to $Context_1$ only. Furthermore, we predicted that this activity would reflect binding to the extent that its magnitude was predictive of subsequent recognition of $Location_1$ in $Context_2$ (not $Location_1$ in $Context_1$), depicted as the thick pink arrow. We hypothesize that the reactivated original location maintained dominance during Passive Refresh (depicted by the thick black border around the white triangle). ***B***, We predicted that ANB (depicted by the pink diagonal bar) would occur during Active Recognition selectively when $Location_2$ was the dominant object location memory when tested in $Context_1$. This is because $Context_1$ was associatively novel with respect to $Location_2$, which had been tied previously to $Context_2$ only. We hypothesize that dominance shifted from the original location to the retrieved location during Active Refresh (depicted by the thick red border around the navy triangle).

eye-movement measures yield the relative amounts of time spent viewing $Location_1$, $Location_2$, and $Location_N$, thus providing continuous measures of location memory maintenance or dominance shift that can be used to categorize every trial. Therefore, dividing trials on the basis of eye movements enabled us to maximize the number of trials allocated to the maintenance and dominance shift conditions, effectively maximizing fMRI signal-to-noise ratio. Second, eye-movement patterns were primarily consistent with recognition selections (Fig. 2*B*), indicating that eye movements provided valid measurements of memory in our paradigm. Furthermore, the allocation of trials to the maintenance and dominance shift conditions based on eye movements was consistent with our other findings that Passive Refresh promoted maintenance whereas Active Refresh promoted dominance shift (Fig. 2*C*), further validating our use of eye movements to capture relevant maintenance and shift effects. Finally, studies have shown that eye movements may be more sensitive to memory than overt selections in some conditions (Hannula and Ranganath, 2009; Hannula et al., 2010; Olsen et al., 2012).

Eye movements were thus used to categorize location-maintenance trials based on the time spent viewing $Location_1$ compared with the time spent viewing $Location_N$ during Recognition. Specifically, location-maintenance trials were those during which the viewing time of $Location_1$ exceeded that of $Location_N$ (Fig. 2*C*). As expected, significantly more trials were categorized as location maintenance for Passive Refresh versus Active Refresh ($t_{(16)} = 2.29$, $p < 0.05$). To identify fMRI correlates of ANB in the Passive Refresh condition, we compared neural activity during Refresh that predicted successful location-memory maintenance in $Context_2$ for the Passive condition, when dominance was maintained, versus the Active condition, when dominance was not maintained. To test for ANB-related activity, we identified activity during Passive Refresh that predicted later location maintenance during Recognition in $Context_2$ (but not in $Context_1$) (Fig. 3). For later Recognition in $Context_2$, the contrast of location-maintenance trials for Passive versus Active Refresh identified enhanced activity in left anterior hippocampus (Fig. 4*A*). Notably, this activity was not identified for later Recognition in $Context_1$ (nor was activity identified anywhere else within hippocampus or MTL for this contrast). This finding is consistent with our prediction that ANB occurred selectively for $Location_1$ and $Context_2$ during Passive Refresh. Activity in other brain regions was identified as predictive of later disproportionate viewing of $Location_1$, although this activity was not selective for later Recognition in $Context_2$ and thus was not related specifically to ANB (Table 1).

We used a similar analysis strategy to test our hypothesis that fMRI correlates of ANB would occur during Recognition after Active Refresh selectively for $Context_1$ (Fig. 3). Location-memory dominance shift was measured as disproportionate viewing of $Location_2$, and trials were categorized as dominance shift when $Location_2$ was viewed more than $Location_N$ (Fig. 2*C*). As expected, significantly more trials were categorized as dominance shift in Active Refresh versus Passive Refresh ($t_{(16)} = 4.52$, $p < 0.001$). Thus, we identified neural activity during Recognition that corresponded to differences in dominance shift in $Context_1$ for Active versus Passive Refresh conditions. Notably, this contrast identified enhanced activity in left anterior hippocampus (Fig. 4*B*), corresponding to the same location that was related to ANB for Passive Refresh (Fig. 4*A*). Activity of the same region was not identified with this contrast for $Context_2$ (nor was activity identified anywhere within hippocampus, MTL, or elsewhere). Enhanced activity associated with updating in $Context_1$ was also identified in other brain regions, especially frontoparie-

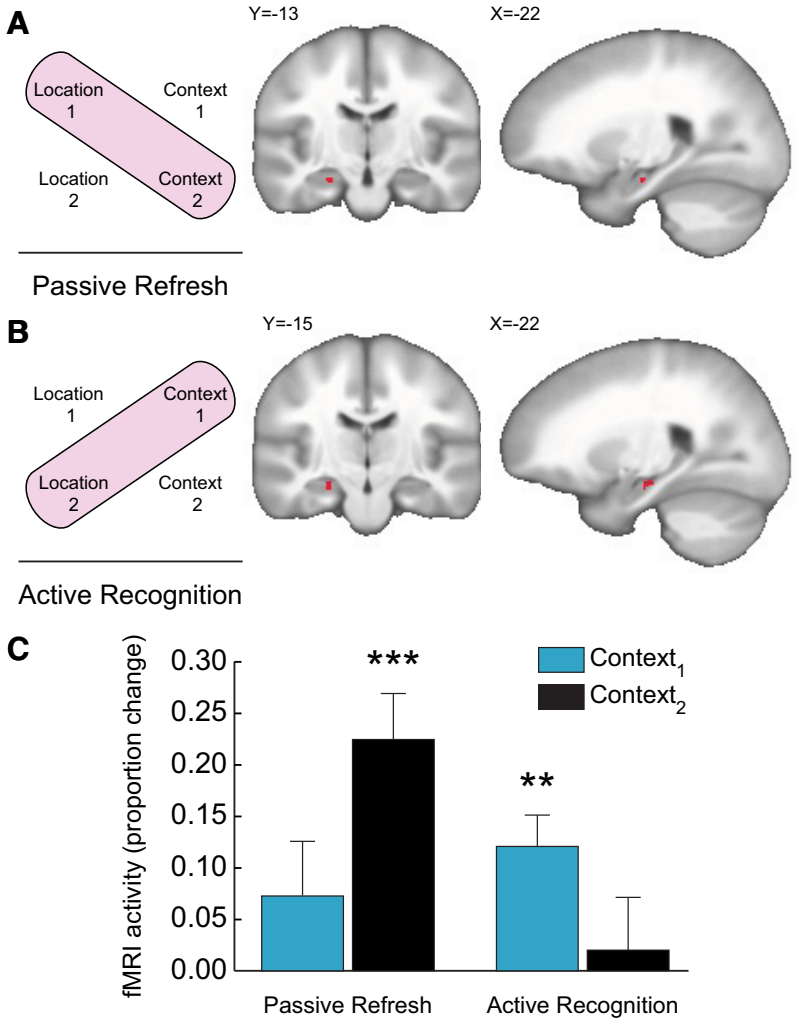

Figure 4. Hippocampal ANB. Binding-related activity occurred when the context was novel with respect to the dominant object-location memory (Fig. 3). ***A***, In the Passive condition, left anterior hippocampal activity during Refresh predicted subsequent memory of $Location_1$ in $Context_2$. ***B***, In the Active condition, left anterior hippocampal activity during Recognition corresponded to memory of $Location_2$ in $Context_1$. ***C***, fMRI signal was extracted from the region encompassed by voxels identified by both of the binding contrasts and was analyzed for each Recognition context separately. Increased hippocampal activity was selective to maintenance of $Location_1$ during Passive Refresh when memory was later tested in $Context_2$. Conversely, hippocampal activity corresponded to memory of $Location_2$ during Recognition in $Context_1$ for the Active condition. Thus, the hippocampus was selectively involved in binding the dominant location memory to the associatively novel context information. *t* tests compared hippocampal differential activity to zero (which would indicate no significant differential activity across conditions). $^{**}p < 0.005$, $^{***}p < 0.001$. Error bars represent SE.

tal cortical regions typically associated with long-term memory encoding and retrieval (Table 1).

Activity in the same left hippocampal location was the only commonality between the two targeted contrasts for ANB. Indeed, investigation of activity within the left hippocampal region common to both contrasts (treated as a single ROI) confirmed this selectivity and linkage to binding of the dominant trace with relatively novel contextual information (Fig. 4*C*). That is, activity predicted subsequent memory of $Location_1$ during Passive Refresh when memory was later tested in $Context_2$ ($t_{(16)} = 4.99$, $p < 0.001$) but not $Context_1$ ($t_{(16)} = 1.36$, NS), and activity corresponded to memory of $Location_2$ during Recognition in the Active condition in $Context_1$ ($t_{(16)} = 3.93$, $p < 0.005$) but not $Context_2$ ($t_{(16)} = 0.39$, NS). These findings support our counterintuitive hypothesis that the same hippocampal ANB supported both object-location memory maintenance and change. This activity indicated novel location-context binding for the dominant trace regardless of whether the binding concerned $Location_1$ with $Context_2$ (during Passive Refresh) or $Location_2$ with $Context_1$ (during Recognition after Active Refresh). Furthermore, this common neural correlate of ANB was identified despite the many differences attributable to the different tasks that were performed during Passive Refresh and Active Recognition (e.g., retrieval-related activity differences, encoding differences, motivational demands, visual stimuli presentation, etc.). In contrast, various brain activations identified outside hippocampus and MTL varied among different contrasts and thus likely reflected these nonspecific factors. It is important to note that activity in this region was not identified by any of the other 28 possible pairwise contrasts among all conditions. Selective identification of hippocampal ANB in only two hypothesized contrasts would be unlikely by chance (i.e., this was identified in one hypothesized contrast pair of 28 possible contrast pairs, and thus possibility of chance occurrence of ~3.6%). Furthermore, the fMRI correlate of ANB occurred for the same hippocampal location in both contrasts, which is remarkable given the possible range of locations within the hippocampus and the rest of the brain. The selectivity of this finding despite all possible nonspecific differences between these two contrasts is difficult to reconcile with any interpretation other than that this hippocampal activity reflected ANB of the dominant trace to the respectively novel context.

Distinction between ANB and dominance shift

We next identified activity associated with the object-location dominance shift that occurred selectively for Active Refresh. Because the dominance shift occurred across contexts selectively for Active Refresh, we identified activity that was greater during Active than Passive Refresh that predicted greater viewing of $Location_2$ (relative to $Location_N$) for Recognition in both $Context_1$ and $Context_2$, which occurred in parahippocampal gyrus (Fig. 5*A*). To determine whether this parahippocampal activity was insensitive to Recognition context, we further scrutinized activity of this region separately for Recognition contexts (Fig. 5*B*). Regardless of whether Recognition later included $Context_1$ ($t_{(16)} = 6.36$, $p < 0.0001$) or $Context_2$ ($t_{(16)} = 4.16$, $p < 0.001$), enhanced activity in the left parahippocampal gyrus predicted subsequent memory of $Location_2$, without significant difference between contexts ($t = 0.71$, NS). Relatively greater activity in frontal cortical and other regions commonly associated with memory retrieval were also identified (Table 1). Thus, dominance shift was not associated with activity in the same left hippocampal location associated with binding but instead occurred with increased activity in distinct MTL regions that have been associated previously with the retrieval of spatial and con-

Table 1. Summary of fMRI activity estimates for primary comparisons

Region	Hemisphere	Volume (mm^3)	*x*	*y*	*z*	Brodmann area
Passive > Active binding during the Refresh phase: $Location_1 \rightarrow Context_2$						
Medial prefrontal gyrus		1502	0	69	22	10
Supramarginal gyrus	Left	1316	−62	−55	25	40
Medial prefrontal gyrus	Right	746	2	60	47	9
Precuneus	Left	729	−12	−54	34	31
Medial prefrontal gyrus	Left	537	−3	61	17	10
Middle temporal gyrus	Left	456	−67	−47	3	22
Inferior temporal gyrus	Left	280	−56	−8	−24	20
Hippocampus*	Left	68	−22	−13	−20	
Passive > Active maintenance during the Refresh phase: $Location_1 \rightarrow Context_1$						
Precuneus	Left	2558	−9	−52	32	31
Supramarginal gyrus	Left	2163	−64	−54	24	40
Medial prefrontal gyrus		1414	0	69	16	10
Middle temporal gyrus	Left	594	−67	−44	3	22
Cerebellum	Right	550	27	−72	−49	
Superior frontal gyrus	Right	368	18	31	61	6
Superior frontal gyrus	Right	354	21	67	29	10
Superior frontal gyrus	Left	290	−16	36	63	8
Active > Passive binding during the Recognition phase: $Location_2 \rightarrow Context_1$						
Superior frontal gyrus	Left	483	−9	1	77	6
Middle frontal gyrus	Left	452	−33	41	49	8
Cerebellum	Left	415	−37	−42	−39	
Superior frontal gyrus	Left	395	−24	52	21	10
Superior frontal gyrus	Right	378	20	9	73	6
Hippocampus*	Left	57	−22	−15	−16	
Active > Passive location-memory dominance shift during the Refresh phase (all contexts)						
Declive/lingual gyrus		9356	0	−86	−22	
Superior frontal gyrus	Left	1823	−1	7	57	6
Precuneus	Left	1772	−9	−83	53	7
Superior frontal gyrus	Left	1455	−31	−7	70	6
Superior frontal gyrus	Right	1168	30	−10	72	6
Precentral gyrus	Left	1107	−42	1	37	6
Inferior frontal gyrus	Left	962	−30	28	7	45
Precuneus	Right	891	14	−80	57	7
Precuneus	Right	351	18	−63	21	31
Precuneus	Right	273	32	−84	43	19
Parahippocampal gyrus*	Left	125	−34	−37	−18	
Parahippocampal gyrus*	Right	71	33	−27	−25	

A combined voxelwise and spatial-extent threshold was used to guard against multiple comparisons. The voxelwise threshold was $p < 0.001$, and the spatial-extent threshold was 268 mm^3 for exploratory whole-brain comparisons ($p < 0.01$ corrected combined threshold) and 51 mm^3 for targeted analysis of MTL regions denoted by *. No suprathreshold clusters were observed in the following contrast: Active > Passive location-memory dominance during the Recognition phase: $Location_2 \geq Context_2$.

figural information (Düzel et al., 2003; Malkova and Mishkin, 2003).

Dominance shift was not related to recall accuracy

We performed an additional control analysis on the behavioral Recognition selections to determine whether the shift in object-location dominance for Active Refresh was merely attributable to poor memory. That is, it may have been the case that the location-memory dominance shift only occurred when recall was relatively inaccurate, i.e., the dominant location memory may have shifted to reflect the $Location_2$ when there was virtually no memory of $Location_1$ during Active Refresh. To assess dominance shift on the basis of recall accuracy, we divided trials based on a median split of the recall error during Active Refresh in each subject. Objects recalled close to $Location_1$ (relatively low error) were those with recall error less than the median error, and objects recalled far from $Location_1$ (relatively high error) were those with recall error greater than the median error. We subjected the proportion of recognition responses to RM-ANOVA with recall error (relatively high, relatively low), test context ($Context_1$, $Context_2$), and location selection during Recognition ($Location_1$, $Location_2$, $Location_N$) as factors. Neither the interaction of recall accuracy and location selection nor the interaction of recall accuracy, location selection, and test context were significant (p values >0.08). Therefore, recall accuracy during the Active refresh phase did not significantly influence the extent to which the location-memory dominance shift occurred. Note that Active Refresh trials with very low recall error were excluded from all analysis because of potential visual overlap during Recognition (see Materials and Methods). Therefore, it is unclear from these results if highly precise memories are susceptible to location-memory dominance shift (but for findings of location-memory dominance shifts regardless of previous recall error using a similar paradigm, see Bridge and Paller, 2012).

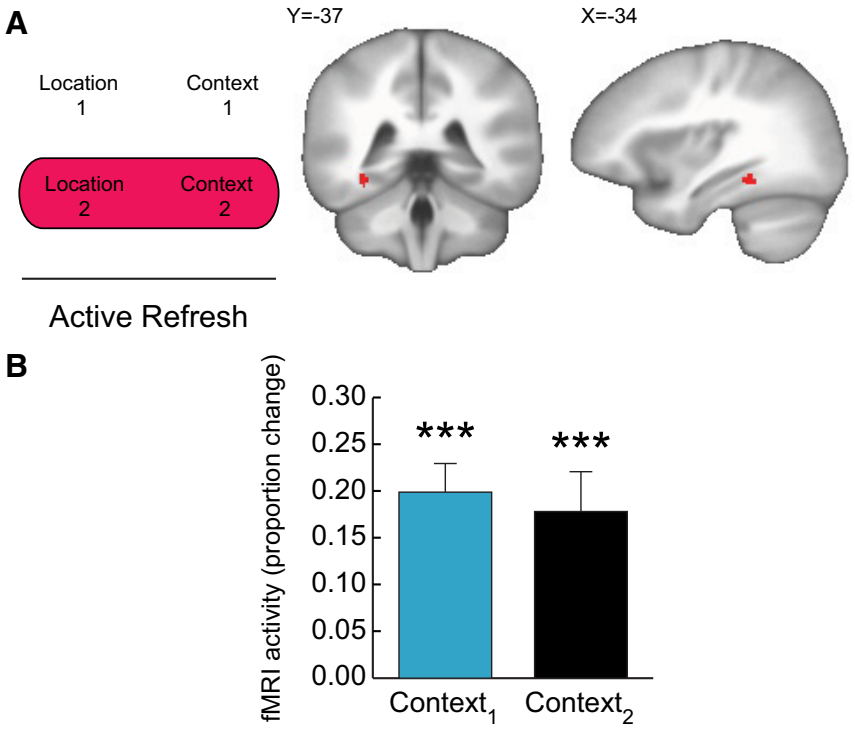

Figure 5. Parahippocampal activity corresponding to dominance shift. ***A***, Activity in MTL cortex was predictive of subsequent memory of Location$_2$ during Active versus Passive Refresh. This activity corresponds to the location-memory dominance shift that occurred selectively for the Active condition and was evident when memory was later tested in either Context$_1$ or Context$_2$. ***B***, Parahippocampal activity predicted location-memory dominance shift regardless of subsequent Recognition context. We created an ROI using the entire parahippocampal region thus identified. We then examined the level of activity in this region on the basis of test context. Activity in this left parahippocampal region was significantly different from zero regardless of whether testing took place in either Context$_1$ or Context$_2$. *t* tests compared parahippocampal gyrus differential activity to zero (which would indicate no significant differential activity across conditions). ***$p < 0.001$. Error bars represent SE.

Discussion

These findings show that hippocampal activity reflecting ANB can support both memory stability and change. Stability resulted when the dominant object-location trace lingered from previous events and was bound via hippocampus to novel contexts, so that it could be remembered in its original form despite changes in context. In contrast, change occurred after the object-location trace shifted dominance and hippocampal binding occurred between the newly dominant trace and a previously encountered context during successful recognition of the dominant trace in the old context. Thus, trace dominance influenced whether memory maintenance versus change occurred, with active retrieval serving as a powerful promoter of shifts in trace dominance. In contrast to hippocampal activity indicating ANB, parahippocampal activity corresponded to trace-dominance shift via active retrieval. These findings extend previous demonstrations of the powerful effects of active retrieval on subsequent memory (Voss et al., 2011; Bridge and Paller, 2012), showing that active retrieval can determine information dominance and therefore whether memory maintenance or change occurs via hippocampal ANB.

Our demonstration of hippocampal ANB links mechanisms of memory updating that have been considered separately in human and animal models. In a seminal study with rodents and fish, Eisenberg et al. (2003) demonstrated that only the dominant trace during reactivation is susceptible to consolidation blockers, suggesting that the dominant trace alone may be temporarily labile and susceptible to disruption, strengthening, or modification during reconsolidation. Subsequent studies have shown that novel environmental information is necessary for the reactivated memory to be susceptible to consolidation blockade (Morris et al., 2006; Winters et al., 2011). These findings suggest that memory modification is critically dependent on two factors: trace dominance and the presence of novel/conflicting information. The hippocampal ANB mechanism we identified in human subjects demonstrates the same properties. This was achieved through the novel paradigm that enabled systematic manipulation of trace dominance in addition to manipulation of whether relatively novel context information was present at different times, across different conditions, and while completing different tasks. This approach enabled us to rule out nonspecific influences on activity, including task-related demands, general encoding and retrieval processes, goal-oriented behavior, and visual stimulus processing. Thus, we show that human hippocampal processing can specifically reflect binding of dominant traces to relatively novel context information, providing an important extension of research on factors that promote reconsolidation in animal models.

These findings also extend the substantial evidence for the role of hippocampus in relational binding operations critical for declarative memory (O'Reilly and Rudy, 2000; Eichenbaum and Cohen, 2001; Norman and O'Reilly, 2003; Eichenbaum et al., 2007; Ranganath, 2010). These accounts emphasize binding of arbitrary elements of complex declarative memories, such as binding item elements to context elements (Ranganath, 2010). Our results add an additional level of specificity in that we identified hippocampal activity specific to ANB of dominant items in memory with contextual information that is relatively novel. Critically, this activity did not merely reflect associative novelty detection (Kumaran and Maguire, 2009) because it was predictive of subsequent memory and therefore reflected ANB rather than mere detection (Bunsey and Eichenbaum, 1996; Honey et al., 1998). Thus, our results demonstrate a role for hippocampus in a specific form of associative/relational binding that is particularly useful for updating dominant traces with novel context information. This binding-related activity was identified in only one portion of the hippocampus (left anterior), and our findings do not exclude involvement of the remaining hippocampus in general associative/relational binding or other functions, which could have occurred during all conditions in our experiment and thus were not identified by our targeted contrasts. The location of ANB activity in the left hippocampal head is consistent with other findings implicating the anterior hippocampus in associative memory encoding (Prince et al., 2005; de Vanssay-Maigne et al., 2011) and associative novelty detection (Kumaran and Maguire, 2007). Given that hippocampal binding-related activity was identified by two separate contrasts that differed in many regards, including any overt demands to learn the association between the dominant trace and the novel

context, our findings also corroborate and extend the idea that hippocampal binding is an automatic and/or obligatory function (Eichenbaum and Cohen, 2001; Olsen et al., 2012).

One potential limitation of our conclusions regarding hippocampal ANB was that memory was not tested after the Recognition phase, and therefore no behavioral measure of the ANB-related hippocampal activity identified during Recognition in the Active condition was provided. Thus, it is possible that hippocampal activity corresponding to memory of $Location_2$ in $Context_1$ during Active Recognition may have merely reflected associative novelty detection rather than binding. However, activity of the same hippocampal location during Passive Refresh reflected ANB based on its selective association with later behavioral measures showing that binding had occurred. Furthermore, the hippocampal activation occurred for $Location_2$ in $Context_1$ during Active Recognition, when binding rather than mere detection should have occurred, but not for $Location_2$ in $Context_1$ during Passive Recognition, when detection but not binding should have occurred (Fig. 3). Therefore, we can infer based on the selectivity of this hippocampal activity across various conditions that it reflected ANB in the Active condition, although future methods including behavioral measures of binding after Active Recognition could provide stronger tests of our interpretations.

Consistent with theorizing that reconsolidation is an instance of continuously active consolidation (Dudai and Eisenberg, 2004; McKenzie and Eichenbaum, 2011; Dudai, 2012), our results suggest that updating via hippocampal ANB may broadly serve as a foundation of memory formation and stabilization. As long as a memory is dependent on hippocampus for access, it is liable to change via the incorporation of novel information. Indeed, memories once thought to become independent of the hippocampus after an extended delay may not actually gain hippocampal independence (Goshen et al., 2011); thus, all memories that were at one time hippocampal dependent may be susceptible to updating after retrieval. Moreover, the hippocampus is required for reconsolidation of object memory after reactivation with novel contextual information (Winters et al., 2011). Thus, a hippocampal-dependent binding mechanism that enables memories to update with new information may be operative when novel contextual information is present during a reactivation event. Retrieval may uniquely influence consolidation by shifting trace dominance and thus making it susceptible to modification. This idea was supported recently by a study that directly stimulated neurons in the hippocampus to induce reactivation of a familiar context memory during contextual fear conditioning in a novel context (Ramirez et al., 2013). Reactivation of the familiar context memory led to the formation of an association between the shock and the familiar context, although these two stimuli were never directly paired. Thus, the hippocampus bridged the old context memory to the learning event in the novel context and updated the original representation with the newly encountered information. Accordingly, memories could be continuously developed, reorganized, and updated during reactivation events at any time point via hippocampal ANB, which occurred here whenever a dominant trace was paired with a context novel to that trace. Importantly, this ANB occurred regardless of the time after initial learning, whether or not "reactivation" was induced, and regardless of the imposed task demands.

Our findings also motivate counterintuitive hypotheses regarding the nature of memory and the ramifications of hippocampal damage. Because hippocampal ANB was involved in memory stability and change, our results suggest that both processes would be impaired in these individuals. Thus, although infiltration of existing memories by newly dominant information is generally considered as memory failure or distortion (Loftus and Pickrell, 1995; Schacter, 2001; Wade et al., 2002; Schacter et al., 2011; but see Schacter et al., 2011), our results suggest that this kind of change is in fact adaptive learning mediated by hippocampal ANB. We would thus predict that hippocampal pathology would impair updating of old memories with newly dominant traces. Although a deficit in ANB could actually help preserve the integrity of old memories (little memory change over time), a negative ramification would be less adaptation of existing memory to suit the needs of the ever-changing environment and therefore poor adaptive behavior. Instances of memory distortion based on newly dominant information may in fact support adaptive function, serving to harmonize memory of past events with current goals and needs. Accounts of memory flexibility have considered mainly how transitive, or conjunctive, representations can support future memory flexibility (Shohamy and Wagner, 2008; Zeithamova and Preston, 2010; Zeithamova et al., 2012). Thus, our results demonstrate a relatively uncharted mechanism whereby hippocampal processing supports flexibility by allowing currently salient information to both project across the different contexts of future circumstances as well as to infiltrate past experiences, such that all memory is adaptively tuned to information that is currently salient. These findings begin to explain a vexing paradox noted more than a century ago by Sigmund Freud that highlights the enduring tension between memory stability and flexibility: "The most important as well as the most peculiar character of psychic fixation consists in the fact that all impressions are on the one hand retained in the same form as they were received, and also in the forms that they have assumed in their further development" (Freud, 1901).

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