Reward Modulation of Hippocampal Subfield Activation during Successful Associative Encoding and Retrieval

Sasha M. Wolosin, Dagmar Zeithamova, and Alison R. Preston

Abstract

■ Emerging evidence suggests that motivation enhances episodic memory formation through interactions between medial-temporal lobe (MTL) structures and dopaminergic midbrain. In addition, recent theories propose that motivation specifically facilitates hippocampal associative binding processes, resulting in more detailed memories that are readily reinstated from partial input. Here, we used high-resolution fMRI to determine how motivation influences associative encoding and retrieval processes within human MTL subregions and dopaminergic midbrain. Participants intentionally encoded object associations under varying conditions of reward and performed a retrieval task during which studied associations were cued from partial input. Behaviorally, cued recall performance was superior for high-value relative to low-value associations; however, participants differed in the degree to which rewards influenced memory. The magnitude of behavioral reward modulation was associated with reward-related activation changes

in dentate gyrus/$CA_{2,3}$ during encoding and enhanced functional connectivity between dentate gyrus/$CA_{2,3}$ and dopaminergic midbrain during both the encoding and retrieval phases of the task. These findings suggests that, within the hippocampus, reward-based motivation specifically enhances dentate gyrus/$CA_{2,3}$ associative encoding mechanisms through interactions with dopaminergic midbrain. Furthermore, within parahippocampal cortex and dopaminergic midbrain regions, activation associated with successful memory formation was modulated by reward across the group. During the retrieval phase, we also observed enhanced activation in hippocampus and dopaminergic midbrain for high-value associations that occurred in the absence of any explicit cues to reward. Collectively, these findings shed light on fundamental mechanisms through which reward impacts associative memory formation and retrieval through facilitation of MTL and ventral tegmental area/substantia nigra processing. ■

INTRODUCTION

Only a small fraction of experiences are remembered. A primary challenge for theories of episodic memory is to understand the psychological processes and neural mechanisms that determine which experiences will be stored in memory. Motivational goals, such as rewards, are a likely driving force in determining whether a particular event will be remembered (Gruber & Otten, 2010; Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006). According to this view, encoding and retrieval processes in medial-temporal lobe (MTL) regions critical to episodic memory (Squire, Stark, & Clark, 2004; Eichenbaum & Cohen, 2001; Gabrieli, 1998) should be subject to motivational influence and reflect enhanced processing of motivationally significant events.

Emerging evidence suggests that interactions between MTL regions and reward-sensitive dopaminergic midbrain (Luo, Tahsili-Fahadan, Wise, Lupica, & Aston-Jones, 2011; Gasbarri, Packard, Campana, & Pacitti, 1994b; Akil & Lewis, 1993; Swanson, 1982) play an important role in episodic memory formation. The midbrain regions that release dopamine—ventral tegmental area (VTA) and

substantia nigra (SN)—target the MTL (Gasbarri, Sulli, & Packard, 1997; Gasbarri, Packard, Campana, & Pacitti, 1994a; Gasbarri, Verney, Innocenzi, Campana, & Pacitti, 1994; Akil & Lewis, 1993) and receive indirect input from MTL regions (Luo et al., 2011; Floresco, West, Ash, Moore, & Grace, 2003; Floresco, Todd, & Grace, 2001; Taepavarapruk, Floresco, & Phillips, 2000; Blaha, Yang, Floresco, Barr, & Phillips, 1997). Neurons within these midbrain regions release dopamine in response to the receipt of a reward as well as to cues that predict reward (Schultz, 1998; Schultz, Apicella, & Ljungberg, 1993). Dopaminergic stimulation of MTL enhances plasticity (Li, Cullen, Anwyl, & Rowan, 2003; Otmakhova & Lisman, 1996), resulting in superior MTL-dependent learning (Granado et al., 2008; Lemon & Manahan-Vaughan, 2006; Bernabeu et al., 1997). In humans, activation of MTL and dopaminergic midbrain is associated with an encoding advantage for individual novel (Wittmann, Bunzeck, Dolan, & Duzel, 2007; Bunzeck & Duzel, 2006) or reward-predicting stimuli (Adcock et al., 2006; Wittmann et al., 2005).

On the basis of such evidence, recent theories have proposed an MTL–midbrain loop whereby dopaminergic signals enhance episodic encoding for salient or rewarding events (Shohamy & Adcock, 2010; Lisman & Grace, 2005). According to these theories, increased dopaminergic drive

associated with rewarding events may enhance plasticity at CA_3–CA_1 synapses to promote memory formation (Lisman & Otmakhova, 2001; Otmakhova & Lisman, 1999). By specifically impacting hippocampal processing, dopamine release may facilitate associative encoding processes that bind event elements together into coherent memory representations (Shohamy & Adcock, 2010); such a mechanism would confer adaptive memory benefits by increasing the likelihood of memory formation and by incorporating motivational information into stored representations. Moreover, reinstatement of motivational salience may play an important role at retrieval by providing additional cues to enable the reconstruction of detailed event information from partial input (Kennedy & Shapiro, 2004, 2009) or by signaling what rewards should be expected during the current experience (Schultz, 1998; Schultz et al., 1993). Recent rodent research suggests that a functional circuit from CA_3 to the VTA (via the lateral septum) plays an important role in reinstating the motivational salience of specific events to guide behavioral choice (Luo et al., 2011).

Despite the importance of this topic for memory research, the neural mechanisms that mediate motivational influences on memory in the human brain are only beginning to be explored. No studies to date have addressed how reward impacts associative memory in human hippocampal subfields. Instead, existing research has focused on motivational influences that impact encoding of individual items using neuroimaging techniques that limit the ability to localize activation to specific hippocampal subregions (Gruber & Otten, 2010; Adcock et al., 2006; Wittmann et al., 2005). These studies thus leave key hypotheses about motivation's influence on associative binding and retrieval processes in the hippocampus untested. Here, we used high-resolution fMRI of the MTL (Carr, Rissman, & Wagner, 2010) to provide a first look at how reward-based motivation influences encoding and retrieval of associative memory through differential engagement of hippocampal subregions. We hypothesized that reward would improve associative binding of event details by specifically enhancing CA_3 encoding processes previously implicated in successful associative binding (e.g., Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Zeineh, Engel, Thompson, & Bookheimer, 2003). In line with recent evidence documenting hippocampally mediated reactivation of value information for highly rewarding events (Kuhl, Shah, DuBrow, & Wagner, 2010), we additionally predicted that enhanced recall of associative information for high-value events would be reflected in hippocampal and midbrain cued recall responses.

It is important to note that sensitivity to reward varies greatly among individuals (Gray, 1987). Individual differences in reward sensitivity have been associated with reward-related neural activation in dopaminergic midbrain regions (Krebs, Schott, & Duzel, 2009), with differences in mesolimbic dopamine function correlating with the degree of learning in reinforcement tasks (Cools et al., 2009; Schonberg, Daw, Joel, & O'Doherty, 2007).

Additionally, individual differences in recognition memory success for highly rewarded stimuli have been shown to correlate with subsequent memory effects (i.e., greater activation for remembered compared with forgotten stimuli) in dopaminergic midbrain (Adcock et al., 2006). Understanding how reward impacts MTL subregional function during associative encoding and retrieval may similarly rely on a characterization of individual differences in behavioral sensitivity to reward. Here, we assessed how individual differences in the degree of reward-based memory modulation (i.e., the relative memory benefit for high-value vs. low-value associations) were related to reward-based modulation of hippocampal subfields and dopaminergic midbrain as well as the functional connectivity between these regions. On the basis of the proposed MTL–midbrain loop, we hypothesized that individual differences in reward modulation of episodic memory would be reflected in enhanced connectivity between dopaminergic midbrain and hippocampus.

METHODS

Participants

Thirty-seven healthy, English-speaking individuals (16 women, aged 18–29 years, mean age = 20 years) were recruited for participation in the fMRI study. All participants were right-handed with normal or corrected-to-normal vision. Before beginning the experiment, participants gave informed consent in accordance with a protocol approved by the institutional review boards of Stanford University and The University of Texas at Austin. Participants received $20/hr for their involvement and additional bonus money based on task performance (up to $34). Data from nine participants were excluded from analysis due to excessive head motion (four participants), an equipment malfunction that resulted in loss of behavioral responses (one participant), and poor performance (four participants). Poor performance was defined as performance 2.5 standard deviations below the group mean, which corresponded to a d-prime of less than 0.75 and a corrected hit rate of less than 0.25 for all trials. All participants included in the analysis had overall task-corrected hit rates of above 0.38 (mean = 0.65, SE = 0.03). Thus, data from 28 participants (11 women, mean age = 21) were included in the fMRI analyses.

Materials

Stimuli consisted of 480 color photographs of common objects organized into 240 object pairs. Object pairs were further organized into high-value and low-value trials (120 pairs in each condition). The presentation of object stimuli across reward conditions and the order of presentation were randomized across participants by assigning each participant to one of eight randomization groups.

Procedures

Encoding

Across eight event-related functional runs, participants intentionally encoded object pairs under varying conditions of reward using a modified version of the monetary incentive encoding task (Adcock et al., 2006). At the beginning of each encoding trial, a fixation dot (0.5 sec) preceded presentation of a monetary cue (1.5 sec) indicating how much money a participant could earn for successfully recalling the association at test (Figure 1A). High-value object pairs were worth $2 if judged correctly at test, whereas low-value object pairs were worth 10¢. Participants were informed that they would be paid 20% of what they earned in the experiment in addition to the base pay of $20/hr. After each monetary cue, a delay period (2 sec) preceded presentation of an object pair (4 sec). During presentation of the object pairs, participants provided a judgment of learning (Kao, Davis, & Gabrieli, 2005), indicating how well they learned each association. These judgments were collected to ensure participants' attention during the encoding phase and were not considered in the analysis of fMRI data.

Each functional encoding run consisted of 15 high-value and 15 low-value trials. A third of the encoding pairs within each run (5 high-value trials and 5 low-value

trials) served as mismatch probes for the cued recall phase. Within each run, associative encoding trials were intermixed with an odd/even digit baseline task (Stark & Squire, 2001) with a total baseline time equal to 25% of total task time. During each 2-sec baseline trial, a single digit between one and eight was presented on the screen and participants indicated whether the digit was odd or even. The order of conditions, including baseline trials, was determined by a sequencing algorithm to optimize the efficiency of the event-related fMRI design (Dale, 1999). The optimization procedure thus ensured that (1) event onsets were not periodic, which is critical for estimation efficiency in fast event-related designs with multiple event types (Liu, Frank, Wong, & Buxton, 2001), and (2) events were jittered by 2-sec intervals so that events either occurred at repetition time (TR) onset or 2 sec after TR onset.

Cued Recall

The experiment alternated between encoding and cued recall phases. An initial set of four encoding runs was followed by four cued recall test runs; a second set of four encoding runs was followed by the final four cued recall runs. On each cued recall trial, a fixation dot (0.5 sec)

Figure 1. Encoding and cued recall tasks. (A) During each encoding trial, participants viewed monetary cues indicating the possible reward for successfully recalling the association at test, followed by a pair of objects. Associative encoding trials were jittered with an odd/even baseline task. (B) During cued recall, a studied object was presented as a cue followed by a delay period during which participants were instructed to recall the learned associate. At the end of the trial, a probe object was presented that was either the correct association (a match) or a studied object that was paired with another object during encoding (a mismatch). After providing a match or mismatch response, participants received feedback regarding their performance. As with encoding, cued recall trials were jittered with an odd/even baseline task.
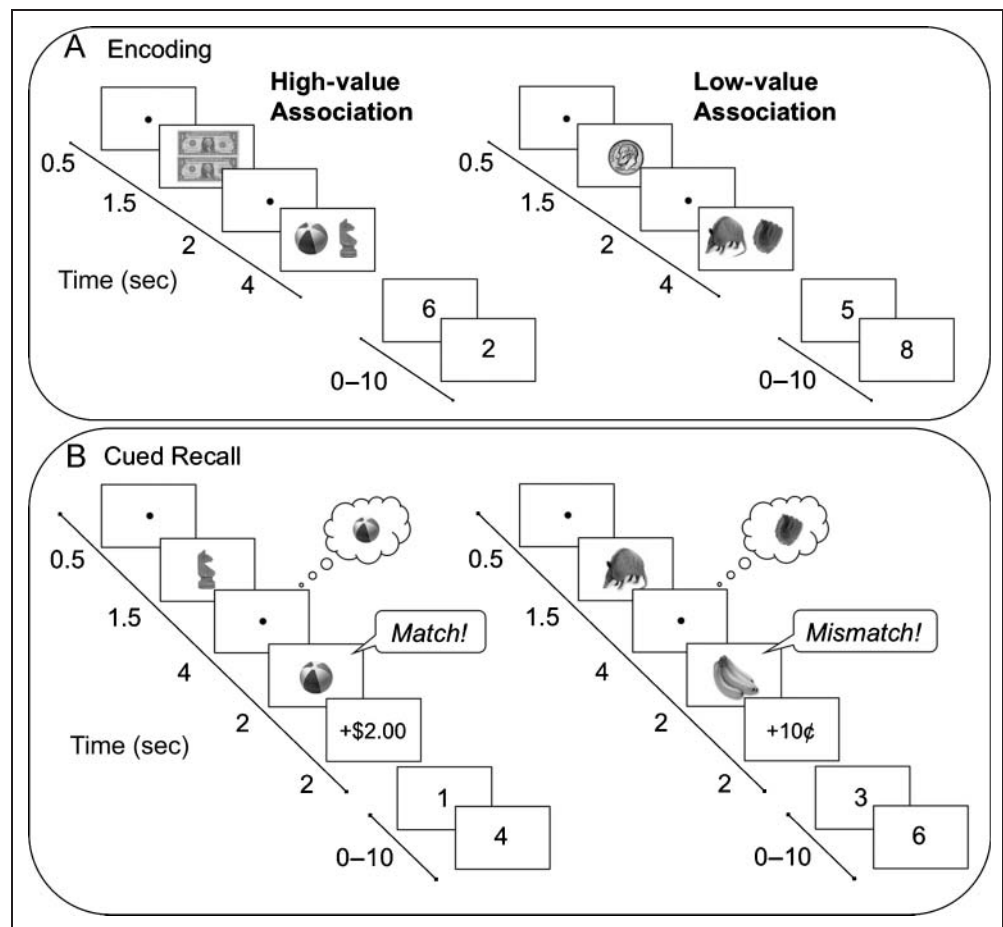
preceded presentation of a previously studied object cue (1.5 sec; Figure 1B). During a delay period (4 sec), participants were instructed to recall and imagine the object associated with the cue. The delay period was followed by a decision probe (2 sec), and participants were asked to judge if the probe was the object originally paired with the cue at encoding (a "match") or another object viewed at encoding, but as part of a different object pair (a "mismatch"). A correct judgment resulted in the receipt of a monetary reward, whereas an incorrect judgment resulted in a corresponding monetary loss. At the end of the trial, participants received feedback (2 sec) about the amount gained or lost on that trial.

The order of object pair presentations within each test run was organized pseudorandomly with the restriction that, within each run, 10 high-value and 10 low-value object pairs were tested. Half of these trials (5 high-value and 5 low-value trials) contained match probes, and the other half contained mismatch probes. After an object from a studied pair was presented either as a retrieval cue or a probe, neither object appeared in subsequent trials. Similar to encoding, 2-sec odd/even digit trials (Stark & Squire, 2001) were intermixed with cued recall trials so that baseline represented 25% of total task time. The order of conditions was determined by a sequencing program to optimize design efficiency (Dale, 1999) and allow for subsampling of the TR.

Stimuli were generated using Matlab (The MathWorks, Inc., Natick, MA) on a MacBook laptop 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 a button pad held in their right hand. Before scanning, participants practiced the encoding and cued recall tasks using stimuli distinct from those presented during functional scanning.

fMRI Acquisition

Imaging data were acquired on a 3.0-T GE Signa whole-body MRI system (GE Medical Systems, Milwaukee, WI) with an eight-channel head coil array. Before functional scanning, high-resolution, T2-weighted, flow-compensated spin-echo structural images (TR = 3 sec, echo time = 68 msec, in-plane resolution = 0.43 × 0.43) were acquired with twenty 3-mm thick slices perpendicular to the main axis of hippocampus to enable visualization of hippocampal subfields, MTL cortical subregions, and midbrain. Functional images were acquired using a high-resolution T2*-sensitive gradient-echo spiral in/out pulse sequence (Glover & Law, 2001), with the same slice locations as the structural images (TR = 4 sec, echo time = 34 msec, flip angle = 80°, field of view = 22 cm, resolution = 1.7 × 1.7 × 3.0 mm). Before functional scanning, a high-order shimming procedure, based on spiral acquisitions, was utilized to reduce B_0 heterogeneity (Kim, Adalsteinsson, Glover, & Spielman, 2002). Critically, spiral in/out methods

are optimized to increase signal-to-noise ratio and BOLD contrast-to-noise ratio in uniform brain regions while reducing signal loss in regions compromised by susceptibility-induced field gradients (Glover & Law, 2001), including the anterior MTL. Compared with other imaging techniques (Glover & Lai, 1998), spiral in/out methods result in less signal dropout and greater task-related activation in MTL (Preston, Thomason, Ochsner, Cooper, & Glover, 2004), allowing targeting of structures that have previously proven difficult to image due to susceptibility-induced field gradient.

A total of 1184 volumes were acquired for each participant (640 during encoding runs and 544 volumes during cued recall). To obtain a field map for correction of magnetic field heterogeneity, the first time frame of the functional times series was collected with an echo time of 2 msec longer than all subsequent frames. For each slice, the map was calculated from the phase of the first two time frames and applied as a first-order correction during reconstruction of the functional images. In this way, blurring and geometric distortion were minimized on a per-slice basis. In addition, correction for off-resonance due to breathing was applied on a per-time-frame basis using phase navigation (Pfeuffer, Van de Moortele, Ugurbil, Hu, & Glover, 2002). This initial volume was then discarded as well as the following two volumes of each scan (a total of 12 sec) to allow for T1 stabilization.

fMRI Analyses

fMRI data were analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) and custom MATLAB routines. T2*-weighted functional 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. Images were then realigned to the first volume of the time series to correct for motion. A mean T2*-weighted functional image was computed during realignment, and the T2-weighted anatomical volume was coregistered to this mean functional volume.

Voxel-based statistical analyses were first conducted at the individual participant level according to the general linear model (Worsley & Friston, 1995). Each phase (encoding and cued recall) was analyzed separately. Regressor functions for each phase were constructed using a finite impulse response (FIR) basis set (2-sec temporal resolution) that began at trial onset and continued 20 sec post-trial onset for encoding trials and 24 sec for cued recall trials. Because the events were intermixed with 2-sec odd/even baseline trials, events either occurred at TR onset or 2 sec after TR onset. Thus, our design was optimized for sampling of the event-related hemodynamic response function with a 2-sec resolution.

To implement voxel-level group analyses for our high-resolution data, we used a nonlinear diffeomorphic

transformation method (Vercauteren, Pennec, Perchant, & Ayache, 2009) implemented in the software package MedINRIA (Version 1.8.0, Asclepios Research Team, France). Specifically, each participant's anatomically defined MTL ROIs were aligned with those of a representative "target" subject using a diffeomorphic deformation algorithm that implements a biologically plausible transformation that respects the boundaries dictated by the anatomical ROIs. As a first step, anatomically defined ROIs were demarcated on the T2-weighted, high-resolution in-plane structural images for each individual participant, using techniques adapted for analysis and visualization of MTL subregions (Preston et al., 2010; Zeineh et al., 2003; Pruessner et al., 2000, 2002; Zeineh, Engel, & Bookheimer, 2000; Insausti et al., 1998; Amaral & Insausti, 1990). Eight MTL subregions were defined in each hemisphere: the hippocampal subfields (dentate gyrus/CA$_{2/3}$, CA$_1$, and subiculum) within the body of the hippocampus and surrounding MTL cortices, including perirhinal cortex (PRc), parahippocampal cortex (PHc), and entorhinal cortex. Because the hippocampal subfields cannot be delineated in the most anterior and posterior extents of the hippocampus at the resolution employed, anterior hippocampal and posterior hippocampal ROIs (inclusive of all subfields) were also demarcated on the most rostral and caudal 1–2 slices of the hippocampus, respectively (Preston et al., 2010; Olsen et al., 2009; Zeineh et al., 2003). These regions roughly correspond to Montreal Neurological Institute coordinates of $y = 0$ to $y = -6$ for the anterior hippocampus and $y = -33$ to $y = -40$ for the posterior hippocampus (Preston et al., 2010).

A single participant's structural images were chosen as the target, and accordingly, all other participants' images were warped into a common space in a manner that maintained the between-region boundaries. To select the target participant, we measured the anterior–posterior length (number of slices) of the MTL for each participant and selected the participant with a length closest to the group average for each hemisphere. This selection process helped to minimize distortion caused by variability in the length of the MTL across participants. To maximize the accuracy of registration within local regions and minimize distortion, separate registrations were performed for left hippocampus, right hippocampus, left MTL cortex, and right MTL cortex. Compared with standard whole-brain normalization techniques, this ROI alignment or "ROI-AL-Demons" approach results in more accurate correspondence of MTL subregions across subjects and higher statistical sensitivity (e.g., Yassa & Stark, 2009; Kirwan, Jones, Miller, & Stark, 2007).

In addition to performing this procedure for the MTL ROIs, a separate normalization was performed for midbrain. Anatomical landmarks, including the red nucleus and superior colliculus (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Oades & Halliday, 1987) were used to align each individual participant's midbrain region to the model subject's midbrain region. The aligned structural images were then normalized using nonlinear diffeomorphic demons. Our ROIs within midbrain included the dopaminergic midbrain regions SN and VTA. As no clear anatomical boundaries delineating SN or VTA can be used to draw a precise ROI, an anterior midbrain mask was drawn on the target structural image using identifiable landmarks on the T2-weighted structural images (see inset in Figure 3A). These landmarks included the red nucleus, identified as a hypointense region near the center of the midbrain, and the anterior boundary of the midbrain. VTA is located medial to and immediately anterior to the red nucleus, whereas SN extends laterally along the anterolateral boundary of the red nucleus (D'Ardenne et al., 2008). On the basis of this anatomical knowledge, the anterior midbrain mask was defined as the region between the posterior end of the red nucleus and the anterior boundary of the midbrain, between the superior and inferior end of the red nucleus.

The transformation matrix generated from the anatomical data for each ROI was then applied to the first-level statistical contrast maps, which enabled second-level group statistical analyses. For all comparisons, group-level statistical maps were first created using an uncorrected voxel-wise threshold of $p < .025$. To correct for multiple comparisons, a small-volume correction was employed to establish a cluster-level corrected threshold of $p < .05$. Small volume correction was determined using Monte Carlo simulations implemented in the AlphaSim tool in AFNI, which takes into account the size and shape of each region, as well as the height threshold p value and smoothness of actual data. Simulations were performed for each region bilaterally (hippocampus, MTL cortex, and VTA/SN). Cluster sizes that occurred with probability of less than 0.05 across 5000 simulations were considered significant. This yielded a minimum cluster size of 32 voxels (108 mm^3) for hippocampus, 37 (125 mm^3) voxels for MTL cortex, and 20 voxels (68 mm^3) for VTA/SN. The resulting group-level results were then localized to specific ROIs to examine condition-specific responses in MTL subregions and VTA/SN.

Functional ROIs were determined by linear contrasts during the stimulus-encoding period (8–12 sec post-trial onset) and during the combined cue and delay period at test (2–6 sec post-trial onset). Four sets of functional ROIs were generated: two sets each from the encoding and test phases. First, to confirm that participants were sensitive to reward manipulation, we identified regions showing greater activation for high-value compared with low-value associations at encoding. We constructed an FIR general linear model containing regressors for high-value and low-value events irrespective of memory status and performed a linear contrast comparing these conditions (high > low) during encoding. The same comparison of high-value and low-value trials was performed for the cue and delay period of the retrieval phase; however, the goal of this contrast at test was to isolate reactivation of reward-related information that occurs in the absence

of explicit cues to reward. Next, to test how reward impacts memory processing in MTL subregions during encoding and cued recall, we isolated regions showing memory success effects (greater activation for remembered compared with forgotten associations) for both the encoding and retrieval phases of the experiment. To do so, we constructed an FIR general linear model containing regressors for remembered and forgotten associations, irrespective of reward status; a linear contrast then compared these event types (remembered > forgotten). Together, these contrasts yielded four sets of functionally defined ROIs: regions that differentiated between (1) high > low during stimulus encoding, (2) remembered > forgotten during stimulus encoding, (3) high > low during cued recall, and (4) remembered > forgotten during cued recall.

For each of the functionally defined ROIs generated from the four contrasts of interest, we then extracted mean beta values for the conditions from the corresponding task phase (encoding, retrieval) using a general linear model that contained regressors for high-value remembered, high-value forgotten, low-value remembered, and low-value forgotten associations. Activation associated with each condition of interest was computed as the average of beta values for the time points corresponding to each event type in the FIR models. Group-level repeated-measures ANOVA with Reward (high-value, low-value) and Memory Status (remembered, forgotten) as factors was used to test for differences in BOLD activity between conditions in each of the ROIs. One participant was excluded from these analyses due to a lack of forgotten associations in the high-value condition.

Additionally, we considered how activation in functionally defined ROIs tracked individual differences in behavior. We were particularly interested in whether behavioral sensitivity to reward (the difference in corrected hit rate for high-value and low-value associations) was related to reward-related changes in brain activation. For each set of functionally defined ROIs, we conducted a multiple regression analysis with the difference in subsequent memory effect (remembered − forgotten) between high-value and low-value pairs (the Memory × Reward interaction) as regressors and behavioral reward modulation as the outcome measure. Because this analysis did not reveal a relationship between the Memory × Reward interaction and behavioral reward modulation of memory in any region, we conducted a similar analysis that was restricted to remembered associations from both reward conditions. Specifically, this analysis assessed how the activation differences for high-value remembered associations relative to low-value remembered associations were related to the degree of behavioral reward modulation across participants. The participant demonstrating ceiling performance on high-value trials was again excluded from the individual differences analyses due to a value for behavioral reward modulation that was greater than three standard deviations from the group mean.

Finally, we were interested in whether individual differences in VTA/SN-MTL connectivity are related to individual differences in behavioral reward modulation of memory. We hypothesized that differences in sustained VTA/SN-MTL connectivity independent of task-based fluctuations would be related to across-participant differences in the degree of behavioral reward modulation of memory, with greater VTA/SN-MTL connectivity for those participants with greater behavioral sensitivity to reward. To test this hypothesis, we examined connectivity between VTA/SN and MTL regions during the encoding and cued recall phases while controlling for common coactivation of these regions due to task-related rewards. We conducted functional connectivity analyses at the individual participant level using a general linear model (Worsley & Friston, 1995) that included the mean activation time course in a seed region (anatomical VTA/SN), regressors respresenting motion parameters, and FIR regressors for each of the four task conditions (high-value remembered, high-value forgotten, low-value remembered, low-value forgotten). Including regressors for the task conditions allowed us to assess how residual intrinsic connectivity between VTA/SN and MTL regions during the encoding and retrieval phases was related to behavioral reward modulation, above and beyond covariation due to task-related differences between individual reward-predicting cues. Separately for encoding and cued recall, we contrasted the VTA/SN seed regressor with baseline to isolate MTL regions that showed a significant sustained connectivity with VTA/SN. The contrast maps from the individual participants were then submitted to a second-level group analysis to determine how connectivity between VTA/SN and MTL varies as a function of behavioral sensitivity to reward. For this analysis, the individual participant functional connectivity maps from the encoding and retrieval phases were weighted by behavioral reward modulation to identify MTL regions for which sustained connectivity between VTA/SN was positively related to the degree of behavioral reward modulation.

RESULTS

Influence of Reward on Memory Performance

The hit rate (correct responses to associative match trials) during cued recall was significantly greater than the false alarm rate (incorrect responses to associative mismatch trials) for both high-value [$t(27) = 20.1, p < .001$] and low-value [$t(27) = 16.1, p < .001$] associations (Figure 2A). Critically, participants showed better memory for high-value associations than low-value associations, as indexed by corrected hit rate (hit rate − false alarm rate; mean ± standard error: high-value = 0.70 ± 0.03, low-value = 0.60 ± 0.04) [$t(27) = 2.28, p < .05$]. This difference in memory was not due to failure to learn the low-value associations, as participants showed above chance performance on the low-value associations across

Figure 2. Behavioral results. (A) Percentage of hits (white bars) and false alarms (gray bars) for high-value and low-value associations. Error bars represent *SEM*. (B) Cued recall performance (as measured by overall corrected hit rate) as a function of behavioral reward modulation (the difference in corrected hit rate for high- and low-value associations). Overall corrected hit rate was not correlated with the degree of behavioral reward modulation ($p > .5$).
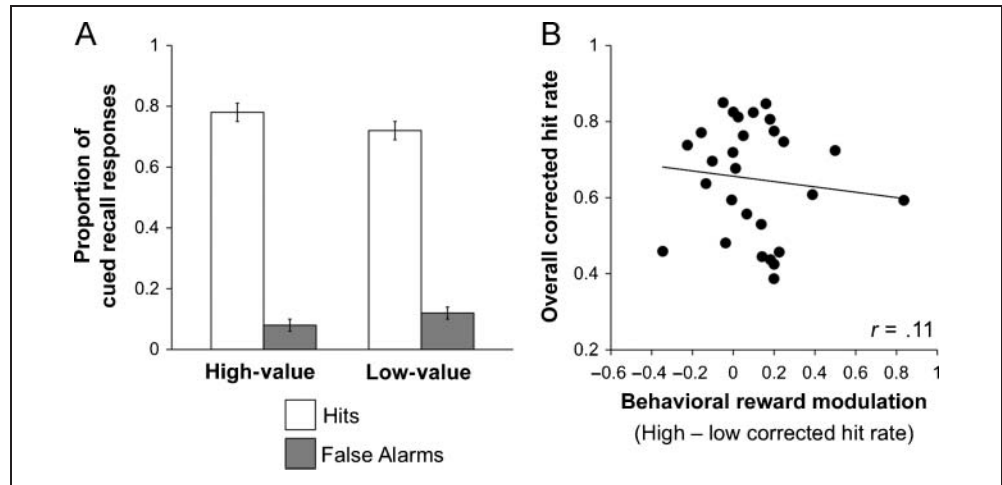
the group [$t(27) = 16.1, p < .001$]. At the level of individual participants, a binomial test revealed that all participants but one showed above chance performance on low-value associations (all $p < .01$); performance for the remaining participant was only marginally above chance on low-value associations ($p = .07$).

Although we observed significantly better memory for high-value relative to low-value associations across the group, there were large individual differences in the degree of reward modulation of memory across participants. To capture these individual differences, we calculated the difference in corrected hit rate between high-value and low-value associations for each participant as an index of behavioral reward modulation of memory. The observed behavioral differences in reward modulation enabled us to explore how individual differences in performance are related to the degree of neural reward modulation within MTL regions and VTA/SN. Importantly, those participants who demonstrated the greatest reward modulation of cued recall performance did not demonstrate the greatest overall memory performance, as the

overall corrected hit rate was not correlated with the degree of behavioral reward modulation ($r = 0.11, p = .59$; Figure 2B). Median RTs during cued recall did not differ between high-value (1031 ± 26 msec) and low-value (1064 ± 28 msec) associations [$t(27) = 1.6, p = .13$].

Regions Differentially Sensitive to Reward during the Encoding Phase

First, to confirm that participants demonstrated neural sensitivity to the reward manipulation, we compared responses for high-value and low-value associations (high > low) during the encoding phase, irrespective of memory performance. This contrast revealed several regions that were differentially sensitive to the reward conditions, including VTA/SN, right PRc, bilateral PHc, and hippocampus, including left CA_1, left subiculum, and bilateral dentate gyrus (DG)/$CA_{2,3}$ (Figure 3). Although these regions demonstrated greater activation for high-value relative to low-value trials, only PHc responses were related to successful associative encoding, as revealed by a
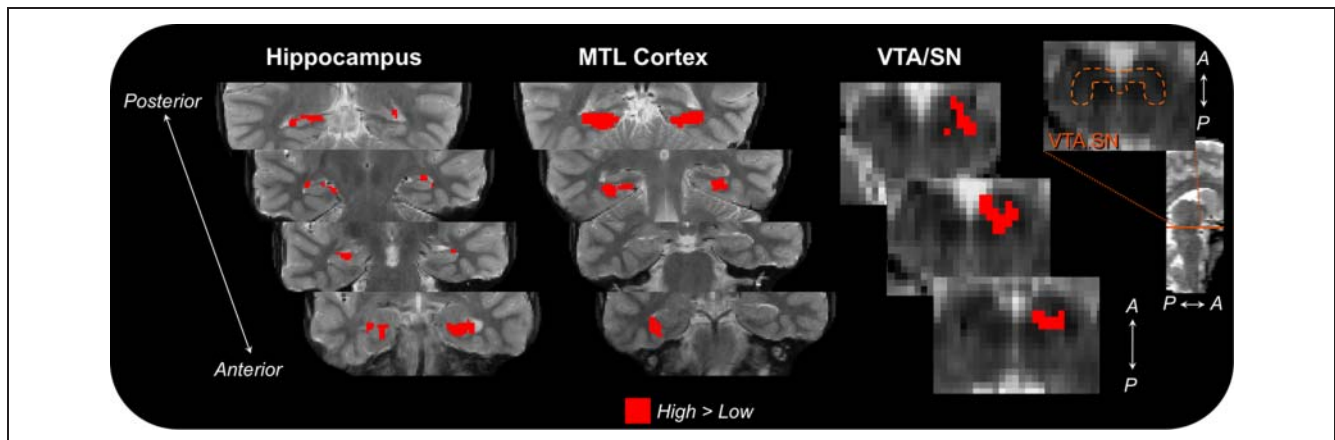

Figure 3. Regions differentially sensitive to reward value during the encoding phase. Encoding activation in VTA/SN and several MTL subregions (shown in red) showed greater activation for high-value relative to low-value associations. An orange-dotted outline indicates the location of VTA/SN on a representative slice.

repeated measures ANOVA with memory (remembered, forgotten) and reward condition (high-value, low-value) as factors. PHc activation showed a main effect of memory in addition to the main effect of reward [all other $F(1, 26) < 3.10, p > .09$], left PHc activation showed a main effect of memory [$F(1, 26) = 4.72, p = .04$], and right PHc activation showed a main effect of memory [$F(1, 26) = 7.42, p = .01$] as well as a Memory $\times$ Reward interaction [$F(1, 26) = 6.02, p = .02$].

Reward Modulation of Successful Memory Formation

The central focus of this study was to understand how reward influences associative encoding processes in

MTL subregions. To do so, we isolated those regions that were related to subsequent memory performance (Paller & Wagner, 2002) by performing a linear contrast comparing activation for remembered and forgotten associations (remembered > forgotten) regardless of reward status during the encoding phase. This contrast revealed a spatially restricted set of MTL regions associated with successful associative encoding, including bilateral CA_1, bilateral $DG/CA_{2,3}$, left subiculum, and bilateral PHc, as well as VTA/SN (Figure 4A). To investigate how monetary incentives influence associative encoding in these memory-sensitive regions, we examined whether subsequent memory effects in these regions were modulated by reward status at encoding, using repeated measures ANOVA with memory (remembered, forgotten) and reward (high-value, low-value) as factors. Encoding activation in right PHc [$F(1,$
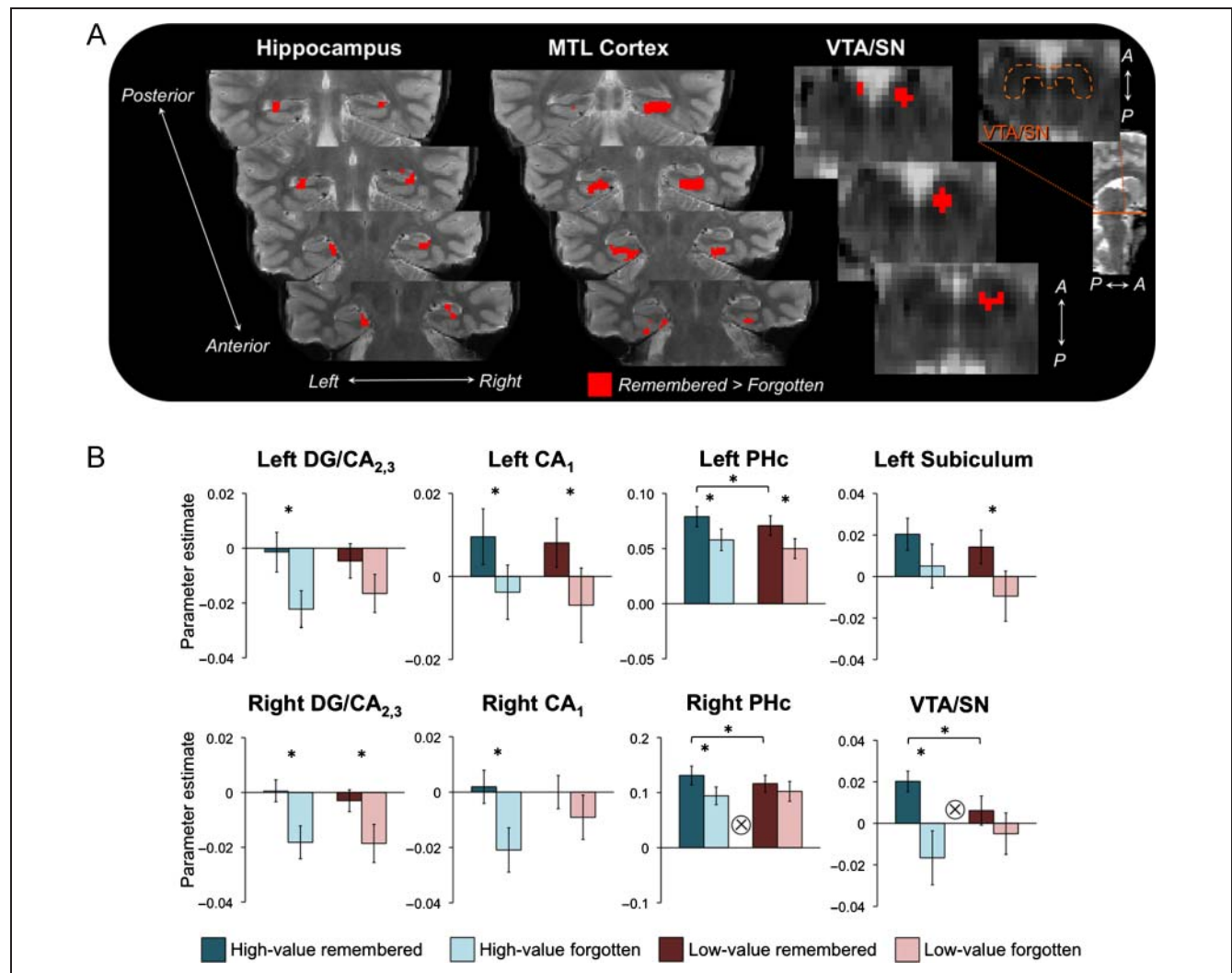

Figure 4. Reward modulation of successful memory formation. (A) Encoding activation in VTA/SN and several MTL subregions (shown in red) was associated with subsequent cued recall performance, with greater activation for remembered relative to forgotten associations. An orange-dotted outline indicates the boundaries of the anatomical VTA/SN region on a representative slice (see Methods for full description of localization procedures). (B) Subsequent memory effects (remembered > forgotten associations) in MTL and VTA/SN plotted as a function of reward value: high-value remembered (dark blue), high-value forgotten (light blue), low-value remembered (red), and low-value forgotten (pink). A significant Reward $\times$ Memory interaction was observed in right PHc and VTA/SN (denoted by a $\otimes$). Error bars represent *SEM*. Asterisks indicate significant pairwise differences ($p < .05$).

26) $= 5.34, p = .03]$ and VTA/SN $[F(1, 26) = 4.89, p = .04]$ showed a significant Memory × Reward interaction, with greater subsequent memory effects for high-value relative to low-value associations (Figure 4B). No other region showed a Memory × Reward interaction [all $F(1, 26) < 2.44, p > .13$] or a main effect of reward [all $F(1, 26) < 3.59, p > .07$].

Notably, we observed large differences in the degree of behavioral reward modulation of memory (the difference in corrected hit rate between high-value and low-value associations) between individuals. Given this behavioral finding, the effect of reward on encoding processes may be best reflected in individual differences in the relationship between subsequent memory effects for high-value relative to low-value associations and the degree of behavioral reward modulation of memory. To test this hypothesis, we assessed how the difference in subsequent memory effects between high-value and low-value pairs (the Memory × Reward interaction) was associated with the degree of behavioral reward modulation of memory across participants. We conducted a multiple regression analysis with the Memory × Reward interaction term for each of the eight subsequent memory regions as regressors and behavioral reward modulation across participants as the outcome measure. We did not observe a positive relationship between the Memory × Reward interaction term and the behavioral reward effect in any region [all $t(18) < 0.80, p > .43$]. However, when we limited our analysis to remembered trials only, we observed a positive relationship between the difference in reward-related activity during successful encoding (high-value remembered − low-value remembered activation) and behavioral reward modulation in right DG/CA$_{2,3}$ [$t(18) = 2.45, p = .03$]. Those participants who showed greater activation for high-value remembered associations relative to low-value remembered associations in right DG/CA$_{2,3}$ demonstrated the greatest behavioral sensitivity to reward (Pearson's $r = 0.41$; Figure 5). The multiple regression analysis did not reveal a positive relationship between activation differences for high-value and low-value remembered associations and the amount of behavioral reward modulation in any other region [all other $t(18) < 1.51, p > .14$].

VTA/SN-MTL Functional Interactions during the Encoding Phase

We hypothesized that behavioral sensitivity to reward would be reflected in across-participant differences in sustained VTA/SN-MTL functional connectivity that are independent of task-based connectivity changes. To examine this hypothesis, we derived individual participant functional connectivity maps from the encoding phase that represented the residual connectivity between VTA/SN and MTL above and beyond task-based covariation in activation. We then submitted these maps to a
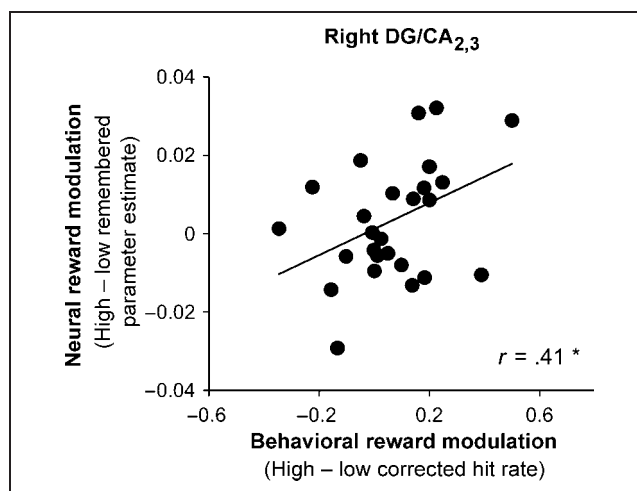

Figure 5. Brain–behavior correlations during associative encoding. We observed a positive relationship between the reward effect for successfully remembered events (high-value remembered parameter estimate − low-value remembered parameter estimate) in DG/CA$_{2,3}$ and behavioral reward modulation of memory (corrected hit rate for high-value trials − corrected hit rate for low-value trials).

second-level regression analysis to determine how sustained connectivity varied as a function of behavioral reward modulation. This analysis revealed activation in bilateral DG/CA$_{2,3}$ for which sustained functional connectivity with VTA/SN was positively correlated with behavioral reward modulation (Figure 6A). This relationship between VTA/SN connectivity and performance was unique to the DG/CA$_{2,3}$, as no other region was identified by this analysis. These results indicate that individuals who demonstrate higher levels of sustained connectivity between VTA/SN and DG/CA$_{2,3}$ throughout the encoding phase of the task are more likely to demonstrate behavioral effects of reward on memory performance.

Regions Differentially Sensitive to Reward during the Retrieval Phase

Although participants did not receive explicit cues to reward during cue and delay period of the cued recall task, we hypothesized that monetary incentives presented during encoding would be reflected in later cued recall activation. To examine this hypothesis, we identified regions showing reward effects (high > low) during the combined cue and delay period at test. This analysis revealed activation in bilateral hippocampus (inclusive of all subfields), bilateral PHc, and VTA/SN (Figure 7A). Repeated measures ANOVA further revealed that, within these regions sensitive to reward status, PHc activation further differentiated trials based on memory success, with greater activation for remembered relative to forgotten associations [main effect of memory: left, $F(1, 26) = 5.66, p = .03$; right, $F(1, 26) = 6.55, p = .02$] (Figure 7B). No other region showed a main effect of memory [all $F(1,$

Figure 6. Sustained functional connectivity between VTA/SN and MTL is associated with behavioral sensitivity to reward during associative encoding and cued recall task phases. (A) Activation in DG/CA$_{2,3}$ (shown in red) for which functional connectivity with VTA/SN was positively correlated with behavioral reward modulation during associative encoding. (B) Activation in DG/CA$_{2,3}$ (shown in red) for which functional connectivity with VTA/SN was positively correlated with behavioral reward modulation during cued recall.
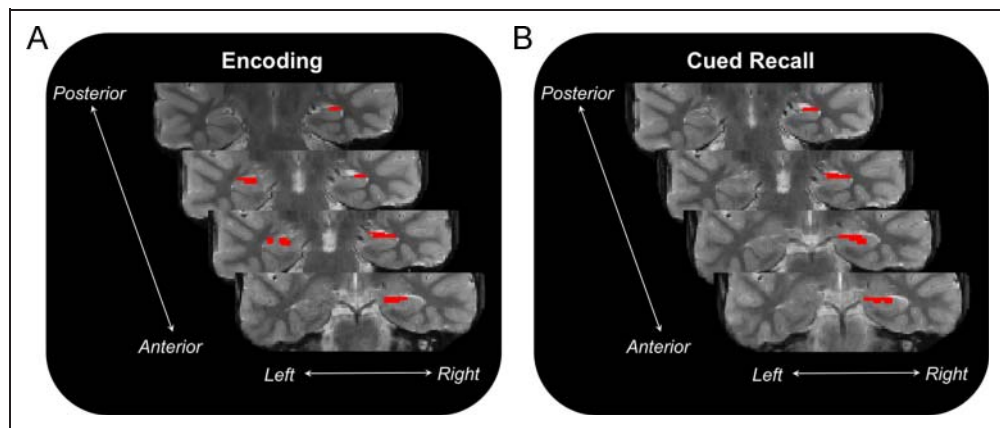
26) < 2.74, $p > .11$], and no region showed a Memory × Reward interaction [all $F(1, 26) < 2.24$, $p > .14$]. These results indicate that reward cues presented during encoding impact later cued recall responses, even in the absence of explicit cues to reward.

Regions Sensitive to Retrieval Success during Cued Recall

To investigate whether monetary incentives presented during associative encoding modulate retrieval success
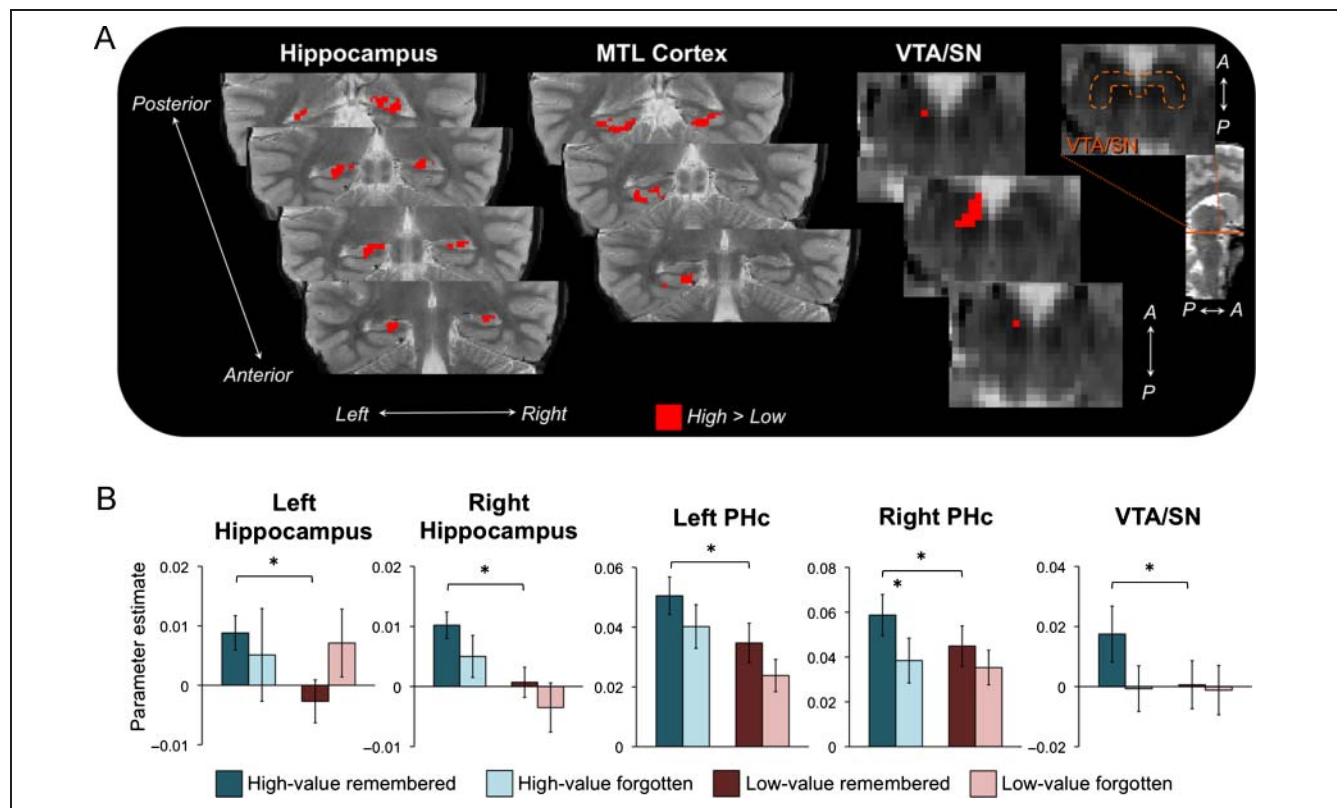

Figure 7. Regions differentially sensitive to reward value during the retrieval phase. (A) Direct comparison of high-value and low-value cued recall trials revealed enhanced activation for high-value information in VTA/SN and MTL subregions (shown in red). An orange-dotted outline indicates the boundaries of the anatomical VTA/SN region on a representative slice. (B) Cue and delay period activation as a function of memory (remembered and forgotten associations) and reward (high- and low-value associations) in MTL and VTA/SN: high-value remembered (dark blue), high-value forgotten (light blue), low-value remembered (red), and low-value forgotten (pink) within regions showing a reward effect (high-value > low-value). Error bars represent *SEM*. Asterisks indicate significant pairwise differences ($p < .05$).
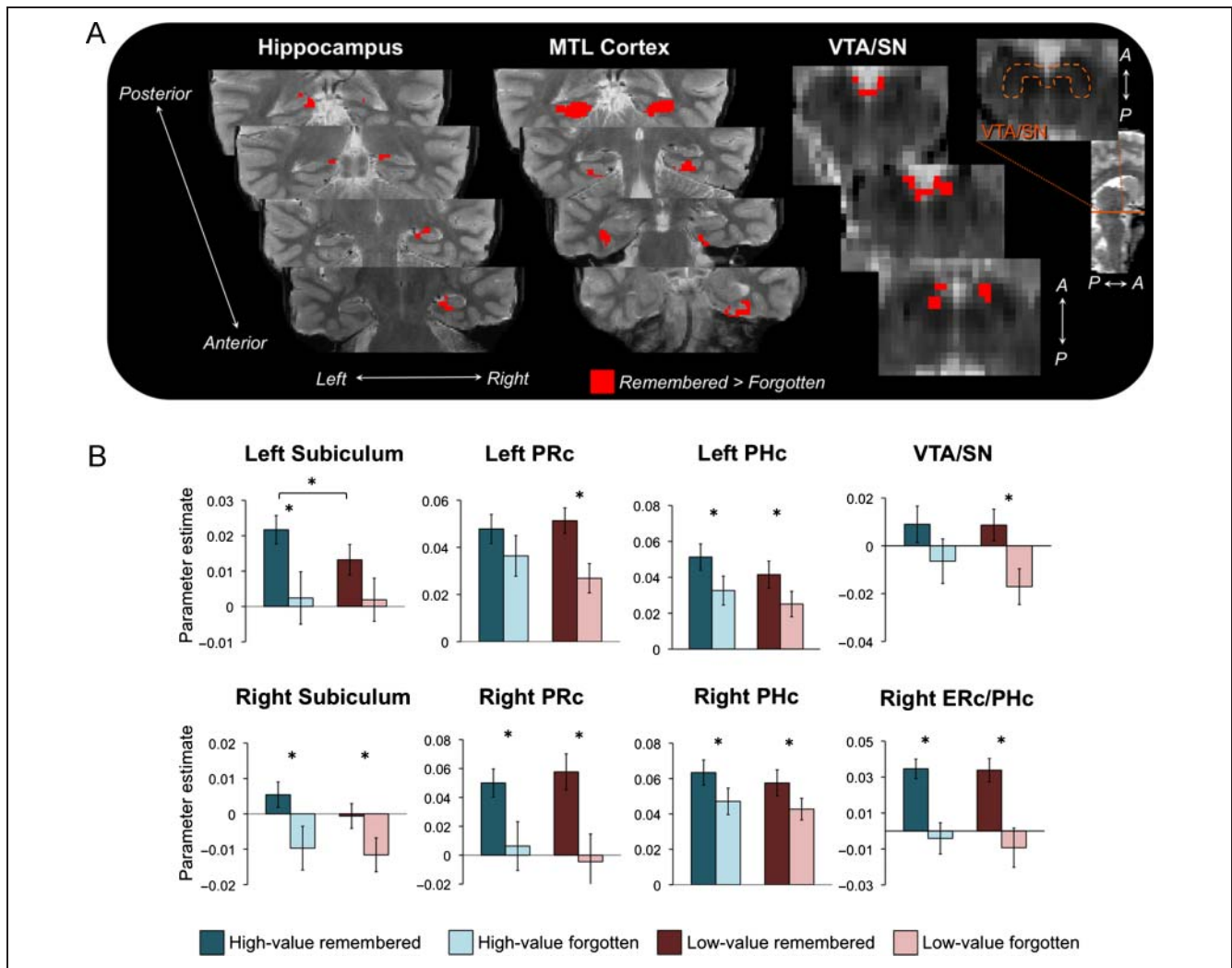
Figure 8. Regions sensitive to retrieval success during cued recall. (A) Cue and delay period activation at test was associated with cued recall success in MTL and VTA/SN (shown in red), with greater activation for successfully recalled relative to forgotten associations. An orange-dotted outline indicates the boundaries of the anatomical VTA/SN region on a representative slice. (B) Retrieval success effects (remembered > forgotten associations) in MTL and VTA/SN plotted as a function of reward value: high-value remembered (dark blue), high-value forgotten (light blue), low-value remembered (red), and low-value forgotten (pink). A significant reward effect for successfully remembered events (high-value remembered parameter estimate − low-value remembered parameter estimate) was observed in left subiculum and left PHc. Error bars represent *SEM*. Asterisks indicate significant pairwise differences ($p < .05$).

effects during cued recall, we identified regions showing retrieval success effects (remembered > forgotten) during the combined cue and delay period at test. This comparison revealed activation in bilateral regions of subiculum, PHc, and PRc, as well as right entorhinal cortex and VTA/SN (Figure 8A) that differentiated between successfully remembered and forgotten associations. None of these retrieval success regions demonstrated a main effect of reward [all $F(1, 26) < 3.41, p > .07$] or a Memory × Reward interaction [all $F(1, 26) < 1.16, p > .29$] (Figure 8B). Multiple regression analysis also revealed that neither the Memory × Reward interaction [$t(18) < 1.20, p > .24$] nor the reward effect for successfully remembered events [$t(18) < 1.56, p > .13$] in these retrieval success regions was related to the degree of behavioral reward modulation across participants. Thus,

although the direct comparison of high-value and low-value associations in the previous section revealed reward-sensitive regions at retrieval, activation in regions sensitive to cued recall success was not modulated by reward. This pattern differs from the encoding phase results and suggests that brain processes and regions that support reinstatement of reward value and retrieval of correct paired associations may be distinct.

VTA/SN-MTL Functional Interactions during the Retrieval Phase

We were also interested in whether behavioral sensitivity to reward was related to individual differences in sustained VTA/SN-MTL connectivity throughout the retrieval phase. Utilizing the same approach applied to the encoding phase

data, we derived maps of sustained VTA/SN-MTL functional connectivity for each individual during the retrieval phase and conducted regression analysis to examine whether individual differences in sustained functional connectivity varied as a function of behavioral reward modulation. This analysis revealed activation in right DG/CA$_{2,3}$ for which sustained functional connectivity with VTA/SN was positively correlated with behavioral reward modulation (Figure 6B). This relationship between VTA/SN connectivity and performance was unique to the DG/CA$_{2,3}$, as no other region was identified by this analysis.

DISCUSSION

Several leading theories propose that motivation plays a key role in the formation of detailed episodic memories through modulation of MTL processing. The current study used the potential of future monetary rewards to examine how motivation impacts associative encoding and retrieval processes in hippocampal and surrounding MTL cortical subregions. Participants were more likely to remember object pairs linked to high-value compared with low-value monetary incentives. Within PHc and VTA/SN, subsequent memory effects were modulated by reward, with greater activation for remembered compared with forgotten associations for high-value but not low-value pairs. Individuals differed in the degree to which reward influenced memory performance; these differences were associated with reward-related changes in DG/CA$_{2,3}$ activation during encoding and greater sustained functional connectivity between DG/CA$_{2,3}$ and VTA/SN during both encoding and retrieval phases of the task. Furthermore, at retrieval, we observed enhanced activation in hippocampus, PHc, and VTA/SN during the combined cue and delay period for high-value relative to low-value associations that occurred in the absence of explicit reward cues. In this study, the use of high-resolution fMRI affords a more detailed view into the neural mechanisms by which motivation impacts associative memory formation in the human brain and characterizes how those mechanisms differ across individuals.

Reward Modulation of Subsequent Memory Effects in PHc and VTA/SN

Several MTL subregions as well as VTA/SN demonstrated sensitivity to reward manipulation during the encoding phase, with greater activation for high-value relative to low-value associations. However, a more spatially restricted set of regions was associated with successful associative encoding across the group, including hippocampal subfields, PHc, and VTA/SN. Within these regions, only right PHc and VTA/SN showed reward modulation of encoding activation, with subsequent memory effects for high-value but not low-value pairs. This interaction pattern suggests

that right PHc and VTA/SN were selectively engaged during high-value trials to promote memory formation.

The present finding that VTA/SN is exclusively engaged during successful encoding of high-value associations is consistent with prior research demonstrating that VTA/SN responses to high-value reward cues before individual item encoding are related to successful subsequent memory (Adcock et al., 2006). This increased activation may reflect enhanced dopamine release from VTA/SN in response to high-value cues when participants are successfully motivated to learn. During high-value forgotten trials, VTA/SN activation was not above baseline, possibly reflecting a lack of motivation on these trials. However, in contrast to Adcock and colleagues, VTA/SN responses observed here were not associated with individual differences in behavior. As discussed below, the reward-related activation in VTA/SN may relate to individual differences in hippocampal activation due to differences in functional connectivity with MTL structures.

Several prior studies have implicated PHc in the binding of associative information (Kirwan & Stark, 2004; Ranganath et al., 2004; Davachi, Mitchell, & Wagner, 2003; Dobbins, Rice, Wagner, & Schacter, 2003; Duzel et al., 2003). The present data extend this work by demonstrating that engagement of PHc associative encoding processes are influenced by reward, leading to superior memory for motivationally significant events. Here, enhanced subsequent memory effects for high-value associations in right PHc could reflect the selective engagement of PHc encoding processes during high-value trials to promote binding of the objects themselves. Alternatively, recent theoretical accounts of MTL function propose that PHc plays an important role in the representation of spatial and nonspatial contextual information surrounding individual events (Aminoff, Gronau, & Bar, 2007; Diana, Yonelinas, & Ranganath, 2007; Davachi, 2006; Bar & Aminoff, 2003). According to this view, enhanced right PHc encoding activation during high-value events may reflect facilitated binding of a specific paired associate to the reward context in which it was presented. Future work that separately indexes memory for item associations and memory for reward context would help to clarify which of these potential PHc binding mechanisms (or both) are reflected in the present findings.

Relationship between DG/CA$_{2,3}$ Activation and Individual Differences in Reward Modulation of Memory

Few studies to date have examined how individual differences in reward sensitivity impact episodic memory through modulation of MTL processing. The present findings demonstrate a high-degree of behavioral variability in the influence of motivational cues on subsequent memory performance. These individual differences in behavioral reward modulation of memory were related to across participant differences in the relative engagement

of DG/CA$_{2,3}$ during the encoding phase, with larger reward-based enhancements in memory performance associated with greater DG/CA$_{2,3}$ activation for high-value remembered relative to low-value remembered associations.

Prior high-resolution fMRI studies in humans have implicated DG/CA$_{2,3}$ in successful associative memory formation (Eldridge et al., 2005; Zeineh et al., 2003), and the present data extend these findings by demonstrating that associative memory processing in this region is subject to motivational influences. One mechanism through which reward impacts memory may be by enhancing learning-related CA$_3$ plasticity (Lisman & Otmakhova, 2001; Otmakhova & Lisman, 1999) that is hypothesized to support the rapid binding of events into integrated memory representations (O'Reilly & Rudy, 2001; McClelland, McNaughton, & O'Reilly, 1995; Marr, 1971). This interpretation is supported by a recent animal study demonstrating reward-related increases in CA$_3$ activity that were enhanced during new associative learning (Singer & Frank, 2009). The present findings suggest that reward exerts a similar influence in human hippocampus, whereby reward-related engagement of CA$_3$ serves to enhance memory for events that lead to future reward.

It is important to note that the relationship between reward-related activation in DG/CA$_{2,3}$ during encoding and behavioral reward modulation of memory was only observed when we restricted our analysis to remembered associations. We did not observe an interaction between reward and subsequent memory effects in DG/CA$_{2,3}$, nor did we observe a correlation between behavioral reward modulation and the degree of reward modulation of subsequent memory effects (the Memory × Reward interaction) in this (or any other) region. Thus, the present findings contrast to some degree with previous results demonstrating reward-related increases in hippocampal subsequent memory effects during item encoding (Adcock et al., 2006; Wittmann et al., 2005). In this study, several possibilities could account for the observation that the relationship between DG/CA$_{2,3}$ activation and individual differences in reward modulation of memory was limited to remembered trials.

One possibility is that signal reductions in the hippocampus relative to PHc in this high-resolution fMRI study (see Liang, Wagner, & Preston, 2012) may limit the ability to observe interaction effects in hippocampal subregions. In addition, performance in this study was well-above chance for high-value and low-value associations, leading to a reduced number of forgotten associations relative to prior studies of individual item encoding (Adcock et al., 2006), which when combined with hippocampal signal reductions would further reduce statistical power. An additional possibility is that the relationship between DG/CA$_{2,3}$ activation and behavioral reward modulation may be biased by the asymmetry in the number of remembered trials between those participants who showed large behavioral effects of reward relative to those who

showed no reward modulation of memory. However, this bias applies to the neural reward effect in all regions, yet only activation in DG/CA$_{2,3}$—a region hypothesized to play a key role in associative encoding—was found to correlate with reward modulation of memory and demonstrate a behaviorally-relevant pattern of functional connectivity with VTA (see below).

Aspects of the present task design that differ from prior related studies may also underlie differences in the observed pattern of hippocampal activation across studies. In particular, Adcock et al. (2006) examined the relationship between reward-related hippocampal activation and subsequent memory performance during an anticipatory phase before individual item encoding. Here, we examined associative encoding, and the present design did not afford the ability to differentiate between the cue period and presentation of the associations.

In addition, and as noted above, participants performed well on both high-value and low-value associations in contrast to prior research. Because DG/CA$_{2,3}$ regions are implicated in successful associative binding, significant DG/CA$_{2,3}$ subsequent memory effects should be expected for high-value and low-value associations, as observed here. Thus, greater DG/CA$_{2,3}$ encoding activation for high-value remembered events relative to low-value remembered events may reflect enhancement of associative encoding processes that are engaged during both event types, but enhanced for high-value trials. One possibility is that enhanced DG/CA$_{2,3}$ processing specific to remembered associations may reflect the formation of stronger or more detailed memory traces for high-value associations than those formed for low-value associations. Follow-up high-resolution fMRI studies could help resolve differences between the present findings and existing research by separately examining cue-related and stimulus-related responses in MTL subregions and by providing more detailed assessments of the quality of successfully formed memories under different motivational conditions.

VTA/SN-DG/CA$_{2,3}$ Functional Connectivity and Individual Differences

The pattern of functional connectivity between DG/CA$_{2,3}$ and VTA/SN further supports the link between DG/CA$_{2,3}$ processing and individual differences in reward modulation of memory. During both the encoding and cued recall phases, greater sustained functional connectivity between VTA/SN and DG/CA$_{2,3}$ was associated with enhanced memory for high-value relative to low-value associations across individuals. Thus, although VTA/SN responses themselves demonstrated sensitivity to reward across the entire group, only those individuals with greater sustained VTA/SN-DG/CA$_{2,3}$ functional connectivity showed behavioral evidence for reward modulation of memory.

Notably, DG/CA$_{2,3}$ was the only MTL region whose connectivity with VTA/SN had a functional relationship

to performance. The localization of the functional connectivity results to DG/CA$_{2,3}$ is consistent with theoretical models and empirical findings that suggest dopaminergic VTA/SN signals facilitate hippocampal processing (Shohamy & Adcock, 2010; Lisman & Grace, 2005) by enhancing CA$_3$ plasticity (Ortiz et al., 2010; Lisman & Otmakhova, 2001; Otmakhova & Lisman, 1999). The present findings provide the first evidence for this proposed mechanism of motivation's influence on memory in the human brain.

It should be emphasized that our specific measure of functional connectivity assessed how sustained VTA/SN connectivity with DG/CA$_{2,3}$ throughout the encoding and retrieval phases was related to performance and was not specific to one particular task condition (e.g., high-value trials). One possible explanation for the present findings is that high-value events yield greater dopamine release in VTA/SN than low-value events in all participants, leading to enhanced VTA/SN activation for high-value associations across the group. However, the impact of VTA/SN activation on MTL responses may differ between individuals. Accordingly, individual differences in sustained VTA/SN-DG/CA$_{2,3}$ functional connectivity may reflect intrinsic differences in the degree of communication between these regions throughout the encoding and cued recall phases. Those participants with greater intrinsic VTA/SN-DG/CA$_{2,3}$ connectivity (as measured by the sustained effects in this study) would be more likely to demonstrate behavioral reward modulation of memory, presumably because of greater reward modulation of DG/CA$_{2,3}$ responses. Although intrinsic connectivity is typically measured during rest, we used a residual connectivity measure that accounted for covariation due to the different task conditions to examine intrinsic differences, as no rest scans were collected in this study. Future work may help to better establish how our measure of sustained connectivity relates to intrinsic functional connectivity measured during rest.

An alternative, but not mutually exclusive, possibility is that associative binding processes in CA$_3$ serve to link particular events with their reward value for both high- and low-value events during encoding, and thus different levels of VTA/SN-DG/CA$_{2,3}$ functional connectivity across participants may reflect the influence of downstream projections from CA$_3$ to VTA/SN via the lateral septum (Luo et al., 2011). Correspondingly, differences in VTA/SN-DG/CA$_{2,3}$ functional connectivity at retrieval may reflect reinstatement of the encoded reward context through CA$_3$ pattern completion processes that target VTA/SN neurons (Luo et al., 2011; Kennedy & Shapiro, 2009). Consistent with this interpretation, the retrieval phase data indicate that monetary incentives presented at encoding are reflected in hippocampal, PHc, and VTA/SN cued recall responses even in the absence of explicit reward cues. Notably, reward-sensitive regions at retrieval were distinct from those demonstrating retrieval success effects, suggesting that reinstatement of reward value and retrieval of item associations are supported by distinct MTL processes. Reactivation of value information in MTL and VTA/SN and enhanced connectivity between regions could establish an expectation of trial outcome (Schultz, 1998; Schultz et al., 1993), such as what probe stimulus should be expected or how much money is at stake, to guide behavioral choice. Alternatively, such enhancements for high-value associations at retrieval could also reflect enhanced re-encoding of retrieved value-pair associations during test (Stark & Okado, 2003).

Conclusions

The present findings indicate that reward-based motivation serves to enhance episodic encoding and retrieval through facilitation of MTL and VTA/SN processing. By specifically influencing associative binding processes in PHc and DG/CA$_{2,3}$, motivational goals may serve to make memories more detailed and flexible, thus better adapted for future use (Shohamy & Adcock, 2010). In particular, this high-resolution fMRI study provides novel insights into the specific mechanisms by which motivation influences episodic memory by linking them to the differential engagement of specific hippocampal and MTL cortical subregions. In doing so, our findings allow for greater convergence with electrophysiological and pharmacological research in animals and provide a foundation for future research aimed at understanding how specific hippocampal-midbrain interactions guide adaptive learning processes that promote the flexible encoding and use of experience.

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