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Reward-Motivated Learning: Mesolimbic Activation Precedes Memory Formation

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Summary

We examined anticipatory mechanisms of reward-motivated memory formation using event-related FMRI. In a monetary incentive encoding task, cues signaled high- or low-value reward for memorizing an upcoming scene. When tested 24 hr postscan, subjects were significantly more likely to remember scenes that followed cues for high-value rather than low-value reward. A monetary incentive delay task independently localized regions responsive to reward anticipation. In the encoding task, high-reward cues preceding remembered but not forgotten scenes activated the ventral tegmental area, nucleus accumbens, and hippocampus. Across subjects, greater activation in these regions predicted superior memory performance. Within subject, increased correlation between the hippocampus and ventral tegmental area was associated with enhanced long-term memory for the subsequent scene. These findings demonstrate that brain activation preceding stimulus encoding can predict declarative memory formation. The findings are consistent with the hypothesis that reward motivation promotes memory formation via dopamine release in the hippocampus prior to learning.

Introduction

The motivation to learn refers to a desire to gain knowledge. It begins before that knowledge is perceived or acquired. In daily life, learning can be inspired by anticipation of remote extrinsic rewards, such as grades, admissions, and promotions; and intrinsic rewards, such as satisfaction of intellectual curiosity. In all of these cases, motivation precedes learning. This implies mechanisms unlike those for stimulus-driven learning (driven by stimulus features such as the novelty, significance, or emotional content) or feedback-driven learning (driven by outcomes that strengthen the association between a stimulus and a response). The goals of this study were to demonstrate motivated learning and to characterize neural systems that support it. We predicted that two neural systems would support motivated learning: a mesolimbic circuit involved in reward anticipation and a medial temporal lobe circuit involved in memory formation.

Midbrain dopamine neurons in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAcc) in the ventral striatum are thought to support reward anticipation. Electrophysiological research indicates that, after reward-based classical conditioning has occurred, VTA dopamine neurons fire in response to cues that predict reward (Schultz, 1998) and during anticipation of reward (Fiorillo et al., 2003). FMRI research indicates that NAcc activation increases in proportion to the magnitude of anticipated reward (Knutson et al., 2001a, 2001b). In rats, stimulating these circuits to release dopamine in the NAcc induces sniffing and other exploratory behaviors that have been likened to curiosity (Ikemoto and Panksepp, 1999). Thus, mesolimbic activation might index a motivational state that could facilitate memory formation.

The medial temporal lobes (or MTL, which include the hippocampus and surrounding cortex) are thought to support declarative memory formation. Damage to the MTL results in global amnesia, which is characterized by diminished or absent declarative memory formation (Scoville and Milner, 1957; Squire, 1992). The magnitude of stimulus-driven MTL activation seen with FMRI following scenes (Brewer et al., 1998), words (Wagner et al., 1998), and line drawings (Wittmann et al., 2005) correlates with later memory for those stimuli.

While not usually considered together, the medial temporal lobes and midbrain dopamine systems are anatomically and functionally related. VTA dopamine neurons directly innervate MTL regions. Intricate region- and layer-specific dopamine projections target the hippocampus (HPC) (Amaral and Cowan, 1980; Lewis et al., 2001; Samson et al., 1990), entorhinal cortex, and perirhinal cortex (Akil and Lewis, 1993). Pharmacological studies suggest that dopamine can modulate MTL-dependent learning. Specifically, in animals, reduced dopamine receptor expression in the MTL (Liu et al., 2004) and midbrain lesions (Gasbarri et al., 1996) impair learning, whereas stimulation of dopamine receptors in the MTL enhances learning (Bernabeu et al., 1997; Jork et al., 1982). Finally, FMRI studies report that novel or reward-predicting stimuli that are later remembered elicit greater midbrain activation than forgotten stimuli (Schott et al., 2004; Wittmann et al., 2005). Taken together, these findings suggest that midbrain dopaminergic systems involved in reward anticipation could directly modulate declarative memory formation in the MTL.

Two lines of physiological research suggest that midbrain modulation of declarative memory would begin even before stimulus presentation. First, dopamine lowers the threshold for long-term potentiation (LTP) if, and only if, it is already available at the synapse when neurons fire (Frey et al., 1993; Huang and Kandel, 1995; Otmakhova and Lisman, 1996), implying prior release. Second, infusion of a dopamine agonist 5 min preceding, but not after, neural stimulation lowers the

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threshold for induction of LTP in the hippocampal area CA1 (Li et al., 2003). These physiological findings suggest the hypothesis that, in motivated learning, VTA activity would precede and potentiate MTL memory formation.

One FMRI study examined incidental memory formation for stimuli that predicted reward (Wittmann et al., 2005). Subjects viewed line drawings of living or nonliving objects, with one set (e.g., living) cuing possible reward. After each drawing, subjects indicated whether it cued reward, then made a number judgment; on reward trials, a fast and accurate response earned money, but a slow or inaccurate response lost money. Following each number judgment, subjects saw feedback indicating gain or loss (reward trials) or no change (neutral trials). On an unexpected memory test 3 weeks later, drawings from the category that cued reward were better remembered than neutral drawings. Neutral drawings did not activate the striatum or midbrain, but reward-predicting drawings did, showing greater activation for those drawings later remembered versus forgotten (i.e., showing an interaction between reward and memory). In an MTL region extending from the hippocampus through the parahippocampal gyrus, there was greater activation for remembered versus forgotten drawings, and for reward-predicting versus neutral drawings, but no interaction between reward and memory. This study provided evidence for a link between midbrain activation and MTL-dependent memory formation.

However, this FMRI study did not address whether motivated learning reflects an interaction between dopaminergic midbrain and MTL regions. First, learning was driven not by prior motivation, but rather by stimulus properties (of the reward-signaling cue itself). Second, the relation between stimulus and reward was reinforced by trial-by-trial feedback. Third, reward and memory formation interactively increased midbrain activation, but not MTL activation. Thus, neither the role of these regions in motivated learning nor the connection between midbrain and MTL activation has been established.

We hypothesized that motivated learning would recruit circuitry related to reward anticipation (i.e., VTA and NAcc) preceding stimulus presentation, and circuitry related to memory formation (i.e., MTL) preceding and during stimulus presentation. Investigators have not yet documented activation that *precedes* a stimulus, but correlates with memory formation for that stimulus. To capture this phenomenon, we performed event-related FMRI during two tasks (Figure 1). First, we localized mesolimbic reward anticipation regions using a monetary incentive delay (MID) task (Knutson et al., 2001a, 2001b), which reliably evokes activation proportional to the amount of anticipated reward in the NAcc and midbrain (Knutson et al., 2005). In the MID task, abstract cues (i.e., circles or squares, with lines indicating amounts from $0 to $5.00) signaled that a subject could gain (or avoid losing) money by rapidly responding to a subsequently presented target; immediate feedback about reward receipt followed each target. Second, we examined reward promotion of memory formation using a monetary incentive encoding (MIE) task, which incorporated reward cues into an intentional memory-encoding paradigm. A high-value ($5.00) or low-value ($0.10) literal cue preceding each memory target indicated the reward for correctly recognizing the target amid foils on a memory test given the next day (Figure 1). Thus, the MIE task separated the motivation to learn from learning itself.

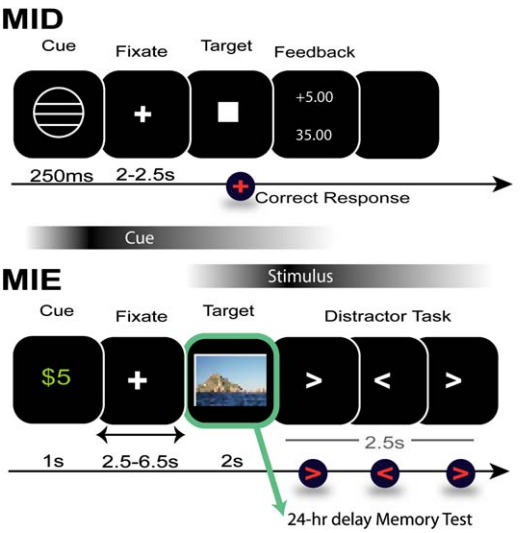

Figure 1. Task Trial Structure

High-value trials are depicted for the monetary incentive delay (MID) task (top) and the monetary incentive encoding (MIE) task (bottom). Gradient bars represent BOLD signals modeled in analyses of each interval. In both tasks, a cue indicated the value of each upcoming target. In the MID task, the correct response was a button press during the rapidly presented target (i.e., a white square). This was followed by feedback about reward and cumulative earnings. In the MIE task, the correct response was recognition of the target scene stimulus at test ~24 hr later. Scenes in the MIE task were followed by a visual-motor distractor task.

Results

Behavioral Results

MID Task

Subjects obtained reward on 73% ± 6% of trials (mean ± SD). Subjects responded more slowly on the +$0.00 trials (reaction time [RT] mean ± SD: 196 ± 12 ms) than on incentive trials [ANOVA main effect of incentive: $F(5,60) = 2.41$, $p = 0.05$; Tukey's LSD pairwise comparisons −$5.00, 181 ± 7 ms, $p = 0.01$; −$1.00, 185 ± 13 ms, $p = 0.04$; +$1.00, 180 ± 15 ms, $p = 0.005$; +$5.00, 183 ± 8 ms, $p = 0.02$]. Hit rate did not vary with incentive.

MIE Arrows Task

Accuracy and RT data for the distractor task following target scenes were submitted to a 2 (memory: high confidence recognized versus forgotten) × 2 (value: high versus low) × 3 (arrow position) ANOVA. There were no significant main effects of memory or value. Collapsed across all conditions, responses to the initial arrow were slower and less accurate [RT: $F(2,10) = 55.5$, $p = .0001$; arrow 1, 498 ± 46 ms; arrow 2, 370 ± 30 ms; arrow 3, 357 ± 24 ms; accuracy: $F(2,10) = 4.15$, $p = 0.05$; arrow 1, 81% ± 16%; arrow 2, 89% ± 12%; arrow 3, 90% ± 10%]. On low-value trials only, RT was slower after recognized versus forgotten targets, but paired comparisons were not significant [arrow × value × memory interaction on RT: $F(2,10) = 5.78$, $p = 0.02$]. On

high-value trials, RT following recognized versus forgotten targets did not differ (low-value trials: forgotten, 489 ± 53 ms, recognized, 519 ± 48 ms; high-value trials: forgotten 512 ± 53 ms; recognized, 520 ± 47 ms).

MIE Recognition Test

Twenty to 26 hours after scanning, subjects (n = 12) recognized both high-value [$t(11) = 14.46$, $p = 1.7 \times 10^{-8}$, paired, two-tailed] and low-value [$t(11) = 7.30$, $p = 1.6 \times 10^{-5}$] scenes presented in the MIE task at significantly greater rates than the false alarm rate (mean ± SD: high-value 70% ± 11%, low-value 60% ± 12%, false alarms 19% ± 10%). As expected, recognition accuracy was greater for high-reward than low-reward scenes [$t(11) = 2.14$, $p = 0.03$, one-tailed]. The reward-driven gain in recognition accuracy was due to increases in correct high-confidence responses (i.e., "Remember" and "Know" pooled), which were significantly more frequent for high- versus low- value scenes [high-value 45% ± 17%, low-value 33% ± 23%, $t(11) = 2.59$, $p = 0.02$, two-tailed]. FMRI analysis was restricted to high-confidence responses. Low-confidence response rates (i.e., "Pretty Sure" and "Guessing" pooled) were not sensitive to reward value (high-value 25% ± 8%, low-value 27% ± 8%).

None of the analyzed subjects reported maintaining a cognitive strategy for preferentially remembering high-value scenes. Across subjects, high- and low-value scene recognitions were positively correlated [$R^2 = 0.43$, $t(11) = 2.7$, $p = 0.07$], suggesting that there was not a strategic tradeoff between learning high- versus low-value stimuli. Because foils were shared for high- and low-value scenes, it is unclear if there were reward-related biases in memory judgments at test, as has been found for emotional stimuli (Sharot et al., 2004).

FMRI Results

Analyses focused on activations in a priori anatomical brain regions associated with reward anticipation, the VTA and NAcc, and with memory formation, the MTL. To test our main hypotheses, we defined functional regions of interest (ROIs) within these anatomical boundaries (for details on boundary demarcation, see Experimental Procedures) at peaks of activation. We extracted individual β coefficients in these ROIs for Cue and Stimulus intervals for each MIE task condition (i.e., each level of reward value [high and low] and memory outcome [recognized and forgotten]) against implicit baseline (i.e., average intensity over the time course; because data were intensity normalized prior to regression, coefficients correspond to percent signal change).

We identified ROIs related to reward anticipation by finding activation peaks in clusters activated during high-value ($5) versus no-value ($0) Cue intervals of the MID task (Table S1 in the Supplemental Data available with this article online; cf. Table S2, reward effects in the MIE task). Our hypothesis was that during MIE task Cue intervals, but not Stimulus intervals, reward anticipation ROIs within the VTA and NAcc would show greater activation for remembered than forgotten items in the high-value, but not the low-value, condition.We also identified ROIs related to memory formation by finding activation peaks in clusters showing greater activation for subsequently recognized versus forgotten scenes in either the Cue or Stimulus interval. Our hypotheses were as follows. (1) Activation of some memory formation regions within the MTL would be influenced by reward, i.e., they would exhibit greater activation for remembered items over forgotten items in the high-value condition but not in the low-value condition, and (2) some MTL areas would have greater activation for high-value remembered versus forgotten trials during the Cue interval, prior to scene presentation.

In addition, we used functional connectivity analysis to examine changes in correlation with VTA seed ROIs as a function of within-subject task conditions. Our hypothesis was that in the hippocampus, correlation with VTA activation would increase both following high-value (versus low-value) cues and preceding recognized (versus forgotten) high-value scenes. Finally, we examined whether memory-related activation of these functional ROIs was correlated across individuals or with individual differences in memory.

ROI Analysis in VTA and NAcc

We found four reward anticipation activation peaks from the MID task in the left and right VTA (Figure 2 and Figure S1), and in the left and right NAcc (Figure 2). For these independently defined ROIs, we submitted individual β coefficients from the MIE task to a 4 (region) × 2 (interval: Cue versus Stimulus) × 2 (value: high versus low) × 2 (memory: recognized versus forgotten) repeated measures ANOVA (Figure 2). In these ROIs, activation showed no main effects of region [$F(3,9) = 0.65$, $p = 0.61$] or interactions with region (all, $p > 0.2$) but did show significant interactions of task conditions with memory [interval × memory interaction, $F(1,11) = 4.98$, $p = 0.047$; interval × reward × memory interaction, $F(1,11) = 5.83$, $p = 0.034$, other effects $p > 0.1$]. These interactions reflect greater activation for recognized versus forgotten scenes only during the Cue interval, and only for high-value scenes (significant paired comparisons of recognized versus forgotten high-value Cue intervals: left [L] VTA, $t = 3.12$, $p = 0.005$; right [R] VTA, $t = 2.48$, $p = 0.02$; L NAcc, $t = 2.61$, $p = 0.01$; R NAcc, $t = 2.72$, $p = 0.01$, one-tailed).

Although ROI definition from MID task activation peaks was independent of MIE analyses, it is possible that choosing ROIs based on activations during reward anticipation biased analyses against finding activations during low-value trials or Stimulus intervals. Whole-brain statistical maps contrasting recognized versus forgotten scenes (at each level of interval and reward value) (Table S3) could identify such activations. Whole-brain analyses did not reveal activations in the VTA or NAcc during low-value Cue intervals or during Stimulus intervals. Thus, alternate methods of defining ROIs would not change inferences about the involvement of the VTA and NAcc in memory formation.

ROI Analysis in MTL

To examine memory formation effects in the MTL, we identified ROIs at activation peaks in whole-brain contrasts of recognized versus forgotten trials during either interval (Tables S3 and S4). These analyses identified five MTL memory ROIs: bilateral anterior hippocampus ("HPC," activated in the Cue interval), right entorhinal cortex ("Ento," activated in the Cue interval), and bilateral posterior parahippocampal cortex ("pPHC," activated in the Stimulus interval). We submitted individual β coefficients to 2 (value: high versus low) × 2 (memory:

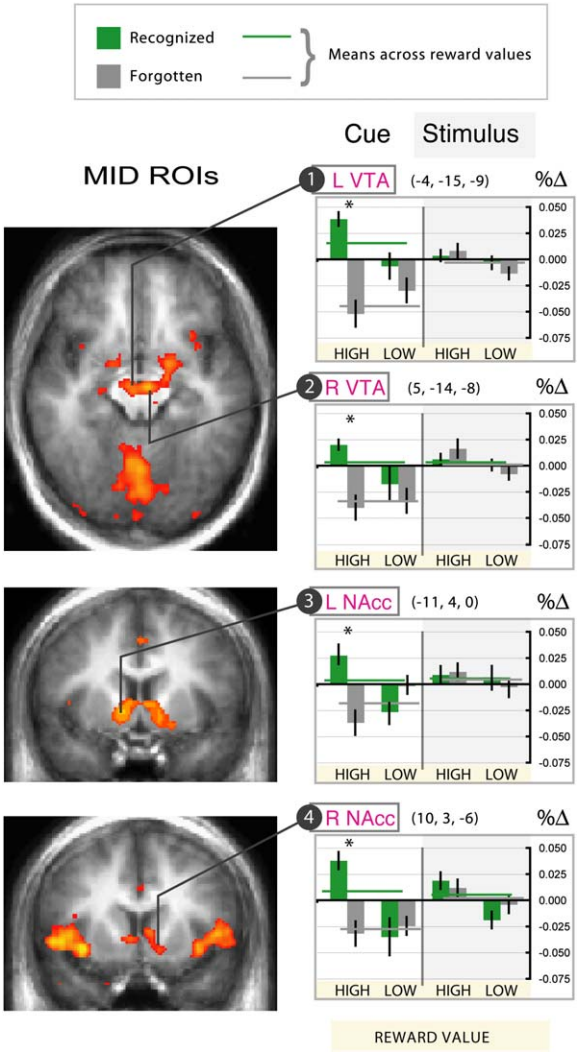

Figure 2. Signal Change across MIE Conditions in the VTA and NAcc

Mean and standard error of individual MIE β coefficients against implicit baseline (percent signal change units) for ROIs defined at peaks in the MID $5 versus $0 contrast in the VTA and NAcc. Asterisks denote significance of paired comparisons between recognized versus forgotten scenes (green versus gray bars, $p < 0.05$). Horizontal green and gray lines show means collapsed across value. For high-value scenes only, activation in all ROIs preceding (in the Cue interval), but not following (in the Stimulus interval), scene presentation predicted whether the scene would be recognized or forgotten at test the next day. Error bars indicate standard error.

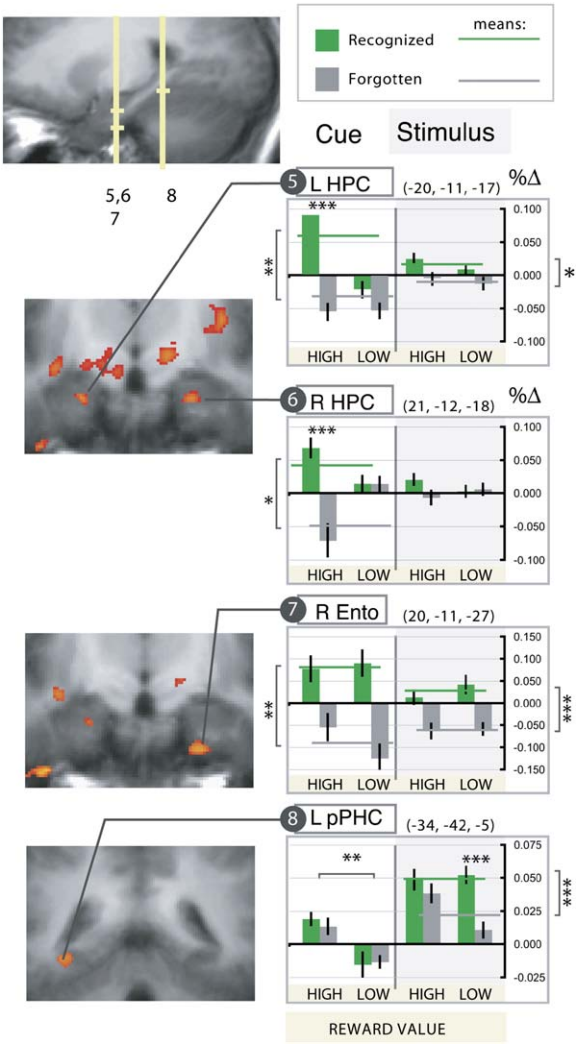

Figure 3. Signal Change across MIE Conditions in the MTL

Mean and standard error of individual β coefficients against implicit baseline (percent signal change units). Memory ROIs in the MTL, indicated in sagittal section (top, x = 21), were defined by recognized versus forgotten contrasts irrespective of reward value (left, contrast maps displayed at $p < 0.005$). (5) Left anterior HPC (L HPC) and (6) right anterior HPC (R HPC), showing a Cue memory effect; (7) right entorhinal cortex (R Ento) showing a main memory effect; (8) left posterior parahippocampal cortex (L pPHC) showing a Stimulus memory effect. Asterisks without brackets denote significance of paired comparisons between recognized versus forgotten (green versus gray bars) scenes at the $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.005$ levels; brackets denote main effects. In the L HPC and R HPC, activation was significantly greater during the Cue interval for recognized versus forgotten high-value scenes, and in the L HPC, activation during the Stimulus interval also showed a memory effect. In the R Ento, activation was related to memory but unrelated to reward value, in both intervals. In the L pPHC, Cue interval activation was greater on high- versus low-value trials but did not predict memory formation, but Stimulus-interval activation was greater for recognized versus forgotten scenes in the low-value condition. Data for (9) contralateral R pPHC (data not shown) were similar. Error bars indicate standard error.

recognized versus forgotten) repeated measures ANOVAs, separately for Cue and Stimulus intervals, to examine reward value effects on memory-related activation. In this analysis, some ROIs exhibited significant activations not seen in the whole-brain analysis, which used more conservative thresholds and cluster size criteria to correct for multiple comparisons.

The L HPC (Figure 3) showed greater activation for recognized versus forgotten high-value scenes during the Cue interval [memory main effect, Cue interval: $F(1,11) = 9.25$, $p = 0.01$; value × memory interaction: $F(1,11) = 5.66$, $p = 0.04$; significant paired comparison of recognized versus forgotten high-value Cue intervals: $t(11) = 3.51$, $p = 0.0025$, one-tailed]. In the ROI analysis, this region also showed significantly greater activation for all recognized scenes during the Stimulus interval [significant memory main effect: $F(1,11) = 5.39$, $p = 0.04$]. The R HPC (Figure 3) showed greater activation for

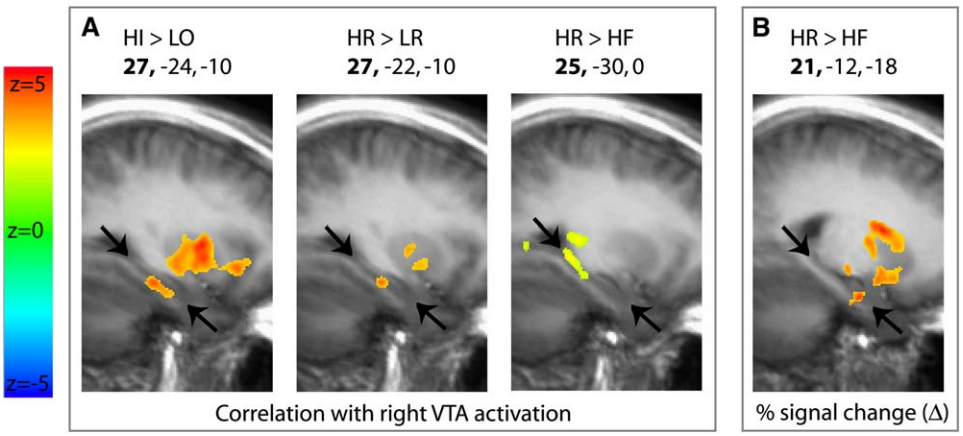

Figure 4. Changes in Hippocampus during the Cue Interval of the MIE Task

Functional connectivity with the VTA (A), and percent signal change ([B], cf. [A], HR > HF). (A) Maps were cluster filtered to achieve an experiment-wise threshold of $p < 0.05$, correcting for combined volume of both hippocampi (2098 mm^3). During Cue intervals preceding high-value versus low-value scenes (HI > LO, $z = 4.17$), correlation with right VTA activation increased in the hippocampus (between arrows). In the subset of trials later recognized (HR > LR, $z = 4.05$), this effect remains significant. (Reward effects were similar in the left hippocampus.) During Cue intervals preceding recognized versus forgotten high-value scenes (HR > HF, $z = 2.55$), correlation with VTA activation increased in the posterior hippocampus. (B) During Cue intervals preceding recognized versus forgotten high-value scenes, percent signal change increases (as measured by β coefficients) were focused in the anterior hippocampus. (For overlap of these effects, see Figure S2.) Activations in the putamen and thalamus are also visible.

recognized versus forgotten high-value scenes only during the Cue interval [significant ANOVA memory main effect, Cue interval: $F(1,11) = 7.70$, $p = 0.018$; value × memory interaction: $F(1,11) = 14.34$, $p = 0.003$, significant paired comparison: $t(11) = 3.94$, $p = 0.001$, one-tailed].

The right entorhinal cortex showed greater activation for all subsequently recognized scenes during both Cue and Stimulus intervals [memory main effect, Cue interval: $F(1,11) = 11.55$, $p = 0.006$; Stimulus interval: $F(1,11) = 13.65$, $p = 0.004$; no interactions]. Left pPHC activation during the Cue interval was not greater for remembered as opposed to forgotten items, but was greater for high- versus low-value scenes [value main effect: $F(1,11) = 8.43$, $p = 0.01$]. Left pPHC Stimulus-interval activation was greater for remembered versus forgotten trials only for low-value scenes [memory main effect: $F(1,11) = 16.51$, $p = 0.002$, value × memory interaction: $F(1,11) = 7.33$, $p = 0.02$; significant paired comparison: $t(11) = 4.60$, $p = 0.0004$, one-tailed]. Right pPHC ([27, −45, −5], not plotted), showed a similar pattern of activation [value main effect, Cue interval: $F(1,11) = 5.93$, $p = 0.03$; memory main effect, Stimulus interval: $F(1,11) = 6.42$, $p = 0.03$; value × memory interaction, Stimulus interval: $F(1,11) = 6.62$, $p = 0.03$; significant paired comparison: $t(11) = 3.54$, $p = 0.002$, one-tailed].

High versus low reward value activated one additional MTL region. Perirhinal/entorhinal cortex (abutting the collateral sulcus [31, −22, −18], data not shown) was activated by high- versus low-value reward but uncorrelated with memory formation [value main effect, Cue interval: $F(1,11) = 32.17$, $p = 0.001$; Stimulus interval: $F(1,11) = 4.03$, $p = 0.07$].

Regional specificity of value and memory effects was confirmed in the four right MTL ROIs via three-way ANOVA interactions within each interval (significant region × value × memory interaction, Cue interval: $F(3,9) = 37.33$, $p = 0.00002$; Stimulus: $F(3,9) = 2.7$, $p = 0.11$), and in a four-way ANOVA interaction (region × interval × value × memory, $F(3,9) = 5.27$, $p = 0.02$). The two left MTL ROIs (HPC and pPHC) showed regional specificity within the Cue interval (significant region × memory interaction, Cue interval: $F(1,11) = 8.7$, $p = 0.01$; Stimulus: n.s.; region × value × memory trend, Cue interval: $F(1,11) = 4.09$, $p = 0.07$; Stimulus: n.s., no region × interval × value × memory interaction).

Functional Connectivity across Conditions

To explore activation correlations between regions, we generated within-subject parametric maps of correlations with seed ROIs in the right and left VTA, hypothesized to be the source of anticipatory activations in the hippocampus. These connectivity analyses reveal regions that vary together trial to trial, thus complementing the group analyses, which identify regions where the magnitude of activation is relatively consistent across trials within a condition. We calculated correlations across trials within a condition, contrasted the correlations in different conditions, and averaged the Z scores from these individual contrasts to obtain group maps. Correlations with the right VTA seed ROI, and to a lesser degree the left (not shown), were sensitive to task conditions (Figure 4). In the hippocampus bilaterally, clusters showed significantly greater correlation with the right VTA after presentation of high- versus low-value cues (peak values in contrast of high- versus low-value, all trials: right, $Z = 4.17$, $p = 0.00002$, at [27, −24, −10]; left, $Z = 2.92$, $p = 0.002$, at [−21, −16, −14]. A similar effect was seen when the high- versus low-value Cue contrast was restricted to recognized scenes (right $Z = 4.05$, $p = 0.00003$, at [27, −22, −10]; left $Z = 3.32$, $p = 0.0004$, at [–22, −17, −9]). After presentation of high-value cues, a cluster in the right hippocampus showed significantly greater correlation with the right VTA preceding recognized versus forgotten scenes ($Z = 2.55$, $p = 0.005$, at [25, −30, 0]). Logical-AND conjunction analysis of regions where increased correlation predicted memory formation AND where magnitude of activation predicted

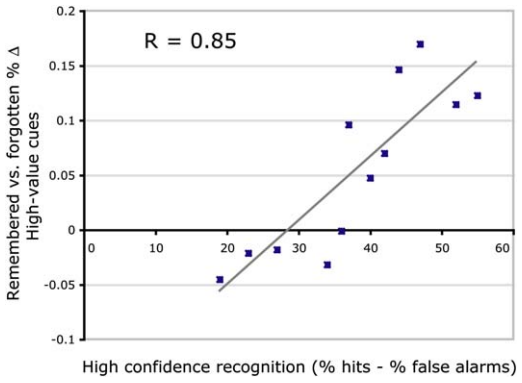

Figure 5. Individual Differences in Activation during the Cue Interval Correlate with Performance

Percent signal change contrast value during the Cue interval for recognized versus forgotten high-value scenes in the right VTA ROI, plotted against individual subjects' high-confidence recognition rate (corrected for high-confidence false alarm rate). R = 0.85, R^2 = 0.73, p = 0.0004.

memory formation identified one significant cluster (81 mm^3) in the right posterior hippocampus (Figure S2). Thus, enhanced correlation between the VTA and hippocampus occurred following high-value cues and prior to remembered scenes. Further, the hippocampal region where enhanced correlation with the VTA predicted memory formation overlapped the region where magnitude of activation predicted memory formation.

Correlations in Functional ROI Activation across Individuals

On high-value trials, Cue interval, memory-related activation in functional ROIs (i.e., the peak contrast value during the Cue interval for recognized versus forgotten scenes) was positively correlated across individuals for the R VTA, R NAcc, and R HPC. The R VTA and R NAcc were significantly correlated (R = 0.74, p = 0.006), and the correlation between the R VTA and R HPC (R = 0.70, p = 0.01) approached corrected significance. The correlation between the R NAcc and R HPC was significant (R = 0.83, = 0.0007), and significantly greater than correlations of the NAcc with entorhinal (R = −0.17; difference p = 0.01) and R pPHC ROIs (R = 0.38; difference p = 0.013). Correlations were not significant during Stimulus intervals or low-value Cue intervals. These correlations indicate that, across subjects, activations preceding high-value remembered scenes were positively and specifically correlated in a right-lateralized VTA-hippocampal-NAcc circuit.

Individual Differences in Memory-Related Activation and Memory Formation

On high-value trials, Cue interval, memory-related activation (i.e., the peak contrast value during the Cue interval for recognized versus forgotten scenes) was positively correlated with recognition memory scores (i.e., high-confidence hit rate, corrected for high-confidence false alarm rates) for functional ROIs in the R VTA (Figure 5; R = 0.85, p = 0.0004) and L NAcc (R = 0.77, p = 0.003), but not the L VTA. In the R NAcc (R = 0.62, p = .03) and R HPC (R = 0.56, p = .05), correlations with later recognition scores approached Bonferroni-corrected significance. Correlations between activation for recognized versus forgotten scenes and later recognition were not significant during Stimulus intervals or low-value Cue intervals. No correlations were significant in the L HPC, entorhinal, or parahippocampal cortex. These correlations indicate that superior recognition for high-value scenes was associated with the magnitude of anticipatory activation in the VTA-hippocampal-NAcc circuit.

Discussion

The present findings identify a neural system that supports motivated learning, promoting memory formation prior to learning on the basis of anticipated reward. Subjects were significantly more likely to remember scenes that followed cues for high-value than low-value reward. High-value reward cues activated the VTA, NAcc, and hippocampus preceding high-value scenes that were later remembered, but not those later forgotten. In the hippocampus, activation was correlated with activation in the VTA, and greater correlation predicted memory formation. In the VTA and NAcc, memory-related activation only preceded stimulus encoding, whereas MTL memory regions also showed memory-related activation during encoding. VTA and NAcc activation preceding high-value scenes correlated with individual differences in recognition memory. Specifically, individuals who showed greater anticipatory activation also showed superior memory.

These results provide initial evidence that brain activation preceding encoding predicts declarative memory formation for subsequent events. Two FMRI studies have shown sustained memory formation states (Fernandez et al., 1999; Otten et al., 2002), but neither isolated the critical activation to the prestimulus period. The results also provide initial evidence linking correlated VTA and hippocampal activation to memory formation. Animal research has shown that dopaminergic inputs from the VTA to the MTL enhance memory formation (Gasbarri et al., 1996) and influence MTL neural activity (Weiss et al., 2003), and conversely, that neural activity in the MTL influences activity in the NAcc (Pennartz and Kitai, 1991; Pennartz et al., 2004; Tabuchi et al., 2000) and the VTA (Floresco et al., 2001; Lodge and Grace, 2005), but previous research has not demonstrated that connectivity of these regions is related to memory. Through both between- and within-subject correlations, the present findings document that connectivity between the VTA and hippocampus, here engaged by reward cues, supports anticipatory memory mechanisms.

Activation Preceding Experience Correlates with Learning

Whereas previous event-related FMRI studies of memory formation have contrasted activation evoked by experiences that were later remembered versus forgotten (Brewer et al., 1998; Wagner et al., 1998; Wittmann et al., 2005), we found that the VTA, NAcc, anterior HPC, and entorhinal cortex were selectively activated *preceding* experiences that were later remembered versus forgotten. One FMRI study reported activation in the entorhinal cortex before, during, and after intentional verbal encoding that was associated with memory formation (Fernandez et al., 1999). The tonic nature of that activation precluded disambiguating whether it reflected

memory processes before or during stimulus presentation. In the present event-related study, it is clear that entorhinal activation was associated with superior memory formation prior to (and during) stimulus presentation. The two studies converge to indicate that the entorhinal cortex may play an important role in state-dependent learning. Further, the present study delineates a neural system that can potentiate memory formation even before a stimulus is encountered. In the VTA, activation was correlated with memory formation *only* prior to stimulus presentation. Importantly, this relationship cannot be explained by properties of the remembered stimulus (e.g., salience or novelty).

Mesolimbic Activation Mediates the Effect of Reward Anticipation on Memory

The present study used a rewarded reaction time task to independently localize neural circuitry activated by reward anticipation and demonstrated that recruitment of the same circuitry correlates with successful memorization. We replicated and extended prior research by demonstrating that anticipation of monetary reward activates not only the NAcc (Knutson et al., 2001a), but also the VTA (cf. Knutson et al., 2005). Although the VTA cannot be directly visualized with MRI, midbrain activations were ventromedial to the directly visualized substantia nigra (Figure S1), consistent with the location of VTA cell bodies, and were accompanied by activations in the hippocampus and NAcc, regions innervated preferentially by the VTA rather than substantia nigra (Amaral and Cowan, 1980; Haber and Fudge, 1997). VTA activation in the MIE task was predicted based on these anatomical relationships, and on evidence that more VTA neurons than nigral neurons fire during reward anticipation in monkeys (Schultz et al., 1993). The present study indicates that VTA and NAcc regions activated by reward anticipation may support a wide range of behaviors, from motor responses to memorization.

We also found an important difference between anticipatory activations in the motor and memory tasks. Whereas MID task activations reflected reward value directly, with greater activation for anticipation of greater reward, activation in the MIE task was increased only preceding high-value scenes that were later recognized. Perhaps the lack of reward feedback and the uncertainty of future reward shifted the source of reward-driven activation from external stimulus-driven processes (in the MID task) to internal goal-driven processes (in the MIE task) that were more vulnerable to other psychological factors, including individual differences. Individuals with greater mesolimbic recruitment had superior memory scores for high-value scenes. Whatever its source, this selectivity suggests that reward anticipation enhanced memory via mesolimbic recruitment.

Potential Mechanisms for Promotion of Memory Formation by Anticipated Reward

A number of physiological mechanisms might underlie the effects of reward anticipation on memory formation. First, like the VTA and NAcc, the hippocampus was selectively activated by high-value cues preceding scenes that were later recognized. Across subjects, the memory-predicting increases in activation in these regions were positively correlated. Furthermore, high-value cues increased correlated activation in the hippocampus and VTA, and greater within-subject correlation predicted memory formation for the subsequent stimulus. These activations identify a mesolimbic circuit (including the VTA, NAcc, and HPC) engaged by reward anticipation prior to memory formation.

Memory-predicting activations in the VTA occurred only prior to stimulus encoding, suggesting that VTA potentiated encoding mechanisms elsewhere. Correlated FMRI activation of the VTA and hippocampus during anticipation could reflect coordinated activity in the VTA and intrinsic hippocampal circuits. In addition to memory-predicting activation during anticipation, the anterior hippocampus also showed memory-predicting activation during stimulus encoding. Thus, the anterior hippocampus is a candidate region where activation of the VTA during reward anticipation could modulate memory formation.

Correlated activation of the VTA and hippocampus could also reflect increased VTA firing (Mukamel et al., 2005) and dopamine release in hippocampal terminals. The BOLD signal appears to be closely correlated with firing rates in active regions (Mukamel et al., 2005). When VTA dopamine neurons increase their firing rates, extracellular dopamine concentrations in VTA targets such as the MTL increase (Garris and Wightman, 1994). Thus, dopamine release in the hippocampus likely accompanied the coordinated activation in the VTA and hippocampus preceding high-value scenes. This sequence (of dopamine release prior to successful memory formation) would agree with reports that dopamine application preceding but not after neural activity lowers the threshold for LTP in the MTL (Frey et al., 1993; Huang and Kandel, 1995; Otmakhova and Lisman, 1996).

Previous subsequent memory studies (of incidental, stimulus-driven encoding) have shown that memory (Brewer et al., 1998; Kirchhoff et al., 2000; Wittmann et al., 2005) and reward (Wittmann et al., 2005) independently activate the posterior parahippocampal cortex. In this region, our observations replicated previous reports. Consistent with prior subsequent memory studies, activation during stimulus encoding was greater for recognized than forgotten pictures. However, this difference was only reliable on low-value trials. Consistent with reward effects observed during incidental encoding (Wittmann et al., 2005), high reward value increased posterior MTL activity on forgotten trials as much as on recognized trials. Thus, although it appears to contribute to stimulus-driven memory mechanisms, the posterior parahippocampal cortex does not appear to be a candidate region where reward anticipation modulates encoding.

In contrast to the specific reward and memory-related responses in the mesolimbic memory circuit, we observed nonspecific reward responses (i.e., for high vs. low reward value but not selective for remembered stimuli) in some MTL regions. Specifically, in the posterior parahippocampal cortex, activation during the Cue interval was greater for forgotten, as well as recognized, high- versus low-value scenes. Outside our memory ROIs, in the perirhinal cortex, activation during both intervals was greater for forgotten, as well as recognized, high- versus low-value scenes. These activations for forgotten as well as recognized scenes might reflect increased effort or attention following high-value cues.

We did not identify behavioral correlates of these reward-related activations: subjects reported abandoning any strategies to preferentially remember high-value scenes within a few trials. Moreover, distractor task reaction times (which might index increased attention or rehearsal of the preceding scene) did not differentiate high- from low-value trials. These unselective (with respect to memory) reward-related activations are important because they indicate that the selectivity for remembered scenes observed in the VTA and NAcc was not due to a failure to perceive or process some high-value cues.

Limitations and Future Directions

The hypothesis proposed here specifically posits a role for dopamine in modulating memory formation. An important caveat is that activation of the VTA probably correlates with the release of not only dopamine, but also other neurotransmitters, such as acetylcholine, which could enhance memory formation in the hippocampus. However, given the extensive electrophysiological data documenting the responsiveness of dopaminergic midbrain neurons to reward cues (Schultz et al., 1993, 1997), it seems unlikely that nondopaminergic midbrain cells would respond to reward cues without concomitant responses in dopamine neurons. Future studies of pharmacological challenges in patient populations and healthy controls, PET binding studies, and animal physiology will help specify the neurotransmitters involved in modulation of declarative memory in motivated learning.

Reward cues could also enhance memory by providing an additional association with the stimulus, allowing easier retrieval. In this associative account, VTA activation is an epiphenomenon resulting from increased cue salience, which leads to enriched encoding. It is unclear why VTA activation would occur for some (in the MIE task) but not all (as in the MID task) high-reward cues, if it reflected salience per se. Future studies that manipulate salience and depth of encoding and test recollection of stimulus reward value could address these questions.

Another open question concerns the localization of reward effects relative to dopaminergic projections. Reward effects and dopaminergic innervation of the MTL (Akil and Lewis, 1993; Akil and Lewis, 1994; Lewis et al., 2001) agree well in some regions (hippocampus and perirhinal cortex) but not in others (entorhinal cortex). Dopamine receptor distributions, another likely determinant of dopamine effects on MTL subregions, show complex gradients with an unclear relationship to dopamine fibers (Goldsmith and Joyce, 1994). High-resolution FMRI studies could help relate activations to gradients of dopamine innervation and receptor density. Further research in primates may be especially important to understanding dopamine's physiological effects in the MTL, because MTL innervation is more robust in primates than in rodents. Finally, in the entorhinal cortex, we observed activation that predicted memory formation both before and during stimulus presentation, regardless of reward value, raising interesting questions about the source and effects of this memory mechanism. Interactions between anticipatory and stimulus-driven mechanisms of memory formation, whether reward-driven or otherwise, are unexplored and may merit further study.

Conclusions

Motivation can precede learning and promote memory formation, independent of stimulus features or feedback. The present study operationalized motivation as potential monetary value for learning, and showed at three different levels of analysis (group effects, individual differences, and intertrial connectivity within subject) that motivation evokes coordinated activation in the VTA and hippocampus preceding memory formation. This mechanism may let an organism's expectations and motivation interact with events in the physical world to influence learning. Thus, anticipatory activation of this mesolimbic circuit may help translate motivation into memory.

Experimental Procedures

Subjects

Volunteers were recruited from the Stanford University community and provided informed consent as indicated by SU IRB-approved protocol. Neuroimaging data are presented for 12 neurologically healthy adults (18–35 years old, three female) who met data quality criteria (described below).

Tasks

FMRI was performed during two tasks: a cued reaction time task (the MID task; Knutson et al., 2001a) to localize activation during reward anticipation; and a memory task, the monetary incentive encoding task. In both tasks, each trial began with a cue indicating the potential monetary reward value of an upcoming target, which appeared after a variable delay (Figure 1). In the MID task, subjects pressed a button during the rapidly presented target, which was followed by immediate feedback. In the MIE task, subjects studied the target, a color photograph of a scene, for a rewarded recognition test the next day, but no rewards or feedback were delivered during the task.

MID Task

Subjects were cued with abstract symbols indicating the reward value of a button press during the upcoming target (a white square). Cue shape signaled potential gain (denoted by circles), potential loss (squares), or no monetary outcome (triangles). The amount at stake was indicated by lines crossing the shape ($0.00, $1.00, or $5.00 for zero, two, or three lines). The target appeared after a variable delay (2–2.5 s). Difficulty was individually titrated after a practice/calibration run to approximate a ~66% hit rate by adjusting the reaction time window for allowed responses. After each target, a feedback screen displayed the reward (for hits) or penalty (for misses) and the cumulative total (Knutson et al., 2001a).

MIE Task

Cues for the reward value of upcoming targets were literal: $5 in green type for high-value or 10¢ in white for low-value conditions. After each cue, a gaze fixation cross (2.5–6.5 s) preceded the mnemonic target scene stimulus (2 s). The number of trials at each delay length was balanced across high- and low-value conditions. Immediately following the target presentation was a visual-motor distractor task, to prevent further elaboration of the target. This "Arrows" task required subjects to indicate the direction of an arrowhead (three trials totaling 2.5 s, arrow duration 667 ms, 250 ms ITI) with a rapid congruent button press. A null period with no fixation cross (4.5–18.5 s) in which subjects were to remain alert for the next cue followed the distractor task. Timing of stimulus onset and ordering of high-value, low-value, and "null trials" was calculated with Optseq software (http://surfer.nmr.mgh.harvard.edu/optseq/).

Target stimuli were color photographs of indoor and outdoor scenes, each novel, subtending a visual angle of ~10° when back-projected onto a plexiglass screen mounted on the head coil. Pictures were pseudorandomly divided into four sets of 60 that contained approximately equal proportions of indoor and outdoor scenes, and subcategories (e.g., beach scenes.) Assignment to study stimuli (OLD, with either high or low value, 60 each) and test distractors (NEW, 120) was counterbalanced across subjects.

Procedure

Prior to scanning, subjects practiced the MID task and the MIE task (complete with recognition test, on a practice set of 20 stimuli not shown during the scanning). Subjects were paid for their practice tests to demonstrate the incentives. The MIE task was imaged in two functional runs each with 60 stimuli in each cue condition (high and low), followed by the MID task. This order was used to avoid affective carryover from the reportedly more exciting MID task. SPGR high-resolution anatomical images were acquired after all functional runs. Subjects performed a recognition memory task for the MIE targets 20–26 hr after scanning, rating both their qualitative memory and confidence.

Subject Instruction

For the MID task, subjects were told that their goal was to earn money by responding with a button press before targets disappeared. For the MIE task, subjects were instructed about reward contingencies and recognition test procedures prior to the practice run. Prior to the scan, subjects were reminded that each trial would begin with the reward value cue followed by a cross, on which they should fixate, to help them remain alert for the upcoming target scene. They were also asked to respond to the arrows as quickly and accurately as they could. At the recognition memory test 24 hr later, subjects were reminded that the 120 OLD pictures were now mixed with 120 NEW distractors and told they would be rewarded for each correct recognition (+$5.00 or +$0.10) and penalized for false alarms (−$2.55). A penalty was included to discourage the strategy of providing an "OLD" response for all the materials. For each item, subjects first pressed a button to indicate whether the scene was NEW or OLD, then responded with a button press to indicate the quality of the memory (i.e., 1 = remember, 2 = know, 3 = pretty sure, 4 = guessing). Subjects were instructed that both 1 and 2 reflected certainty that the scene had been studied, and to indicate Remember if they remembered the moment they had encountered the item, or Know if they felt sure the item had been presented but did not have a specific memory of the episode. Subjects were told that ratings did not affect compensation. In order to minimize the influence of guessing on the subsequent memory analysis, only items rated as Remembered or Known, or items that were actually forgotten (misses) were analyzed.

MRI Data Acquisition

Data were acquired on a 3.0T GE Signa scanner using a head coil with bite bar. Functional data were collected using T2* spiral in/out sequence (Glover and Law, 2001) to minimize signal dropout in ventral regions of interest (TE 30, flip 60.) Volumes were acquired at a TR of 1 s in 15 contiguous 5 mm oblique slices (voxel size 3.44 mm × 3.44 mm × 5 mm, 59 mm^3). The inferior edge of the acquired volume was aligned with the frontal and temporal poles and the volume extended superior to the retrosplenial cortex. MIE task data were acquired in two runs totaling 1960 volumes (16 min 20 s). MID task data were acquired in one run of 540 volumes (9 min). The first six volumes of each run were discarded to allow magnetic stabilization. T1- and T2-weighted anatomical images were acquired in the same prescription as functional data. SPGR anatomical data were acquired in 128 contiguous 1.5 mm slices perpendicular to the long axis of the HPC.

FMRI Data Analysis

Data Quality Assessment and Preprocessing

Data from two scanned subjects was excluded for behavioral noncompliance: one closed his eyes during low-value trials, and the second misunderstood the recognition test rules. Data from four scanned subjects were excluded for motion (one subject) or sustained image artifacts (three subjects).

Data were visually inspected and reviewed for artifacts and motion using custom software (http://web.mit.edu/swg/www/tools.htm). Functional data were analyzed only if they exhibited less than 1 mm motion (absolute maximum). Actual motion was less than 0.5 mm through three translations and rotations and not task correlated (max. R = 0.032). Images with transient noise artifacts (greater than 1.5 SD from mean) were excluded from analysis (fewer than six per subject.)

The FMRIB Software Library (FSL) BET tool (http://www.fmrib.ox.ac.uk/fsl) was used to generate skull-stripped anatomical images. SPM2 (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/spm2.html) was used for automated initial coregistration of SPGR anatomical images to T1-weighted in-plane anatomicals and for slice timing correction (to slice seven). Images were then imported to AFNI (Cox, 1996) for further preprocessing, involving the following steps: coregistration of the subject's in-plane T1 to an averaged functional image, motion calculation, spatial smoothing with a 4 mm FWHM Gaussian kernel, and voxelwise intensity normalization to percent signal change. This smoothing kernel was chosen to optimize differentiation of midbrain and ventral striatal activations. In preparation for group-level analyses, Talairach transforms were determined on skull-stripped high-resolution anatomical images and applied to coregistered in-plane anatomicals and statistical parametric maps. Maps were resampled to 1 mm^3 voxels during spatial normalization.

Statistical Analysis

Individual GLM-based analyses were conducted in original space. Models included regressors of interest generated by convolving task events with a γ function model of the hemodynamic response (Cohen, 1997), as well as nuisance regressors modeling baseline (modeled on Legendre polynomials) and motion.

For the MID task, analyses replicated those in previous publications (Hommer et al., 2003; Knutson et al., 2001a, 2003). First-level regressors of interest incorporated contrasts between anticipation of gain versus nongain targets ($1.00 and $5.00 versus $0.00) and high versus low gain ($5.00 versus $1.00) targets. Loss trials were not included in the current analysis. β coefficients were converted to Z scores, Talairach transformed, and averaged using a meta-analytic formula.

For the MIE task, β coefficients were estimated within each interval (Cue, Stimulus) relative to implicit baseline (the average intensity across all trials). Because data were intensity normalized prior to regression, β coefficients are in units of percent signal change. Trials were sorted by level of reward value and by recognized (highest confidence ratings only) and forgotten outcome (i.e., High-value Recognized, High-value Forgotten, Low-value Recognized, Low-value Forgotten.) Talairach-warped maps of individuals' β coefficients for each condition were submitted to a two-way group ANOVA with trial type as fixed and individuals as random effects. Paired voxel-wise t contrasts were conducted within AFNI, with main effects of value and memory assessed by contrasts collapsing across levels. Interval, value, and memory effects and their interactions were further assessed in ROI data by repeated measures ANOVAs, as described in the Results section.

Excluding Cue interval regressors from the model did not affect inferences for the Stimulus interval. T values reported for Stimulus interval contrasts are from the Stimulus-alone regression, because this most closely parallels analyses in prior memory literature.

Localization and Criteria for Reporting Activation

MID task maps were used to localize regions activated during reward anticipation, in particular the VTA, for which anatomical criteria alone are ambiguous, and to generate unbiased reward anticipation-responsive ROIs for interrogation of data collected during the MIE task. Activation peaks that fell within anatomically identified a priori regions were used to define ROIs. These a priori regions included the VTA, substantia nigra, NAcc, anterior HPC, entorhinal cortex, perirhinal/entorhinal cortex, posterior HPC, and posterior parahippocampal cortex. Anatomical landmarks for all ROIs were directly visualized in the averaged high-resolution anatomical image and verified in individual anatomical data. Landmarks for striatal structures followed (Breiter et al., 1997). Landmarks for MTL structures followed (Pruessner et al., 2002), except "perirhinal/entorhinal" designates activations that include the collateral sulcus, and "entorhinal" is reserved for activations that do not (given resolution limits of averaged anatomy). The VTA was identified medial and anterior to the substantia nigra.

For contrasts in the MIE task, activations are reported using two methods. For identification of activations outside hypothesized regions, data were thresholded at $p < 0.005$ and submitted to automated cluster detection within AFNI (minimum volume 354 mm^3). This spatial extent correction for multiple comparisons corresponds to an overall $\alpha < 0.05$ FWE rate, as calculated with AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/), with 1000 Monte Carlo simulations and 4 mm FWHM smoothness for all intracranial voxels in the

imaged volume. (The corresponding correction for data thresholded at $p < 0.001$ was 236 mm^3.) Activations were inspected to ensure they did not overlie large vessels and to detect multiple peaks within clusters.

In regions identified by a priori hypothesis, activations were identified by the intersection of functional activation and anatomical boundaries. Data within a priori regions of interest are reported thresholded at $p < 0.001$ (uncorrected) for the High Cue interval contrasts critical to our hypotheses. For main effects and Stimulus interval contrasts, a threshold of $p < 0.005$ was used, as it approximated activation extents seen at $p < 0.001$ in the critical contrasts.

Given the heterogeneous anatomy of basal ganglia and MTL structures, spatial extent corrections calculated with respect to all brain voxels might obscure meaningful distinctions within these regions. We reported smaller clusters in these areas if they met four additional criteria: (1) volume greater than two original-sized voxels or 118 mm^3, (2) peak significance greater than $p < 0.0005$, (3) localization entirely within one anatomical region, and (4) peak significance greater at 4 mm smoothing than at 6 or 8 mm smoothing. Three such small clusters were identified, denoted by actual volume in the tables.

ROI Analyses

For each individual, we extracted β coefficients (in units of percent signal change) by condition, relative to implicit baseline (time course average) at group contrast identified activation peaks within a priori anatomical boundaries. Derivation of MID reward anticipation ROIs in the VTA and NAcc was independent of MIE task analyses. Derivation of memory ROIs was independent of reward value. In addition to those plotted, we examined one subthreshold peak (in whole-brain contrast of recognized versus forgotten Stimulus intervals, significance $p < 0.005$ uncorrected) in the right pPHC, implicated in scene encoding by prior reports. In all functional ROIs, repeated measures ANOVAs examined interactions between region, interval, reward value, and memory outcome. Across individuals, we also used these ROIs to test correlations between recognized versus forgotten contrast values for pairs of ROIs, and between contrast values and memory performance (Pearson's r). Significance of correlations was tested with two-tailed Student's t tests against zero and against other correlations.

Functional Connectivity with Reward Anticipation ROIs

To explore the correlations between hippocampus and mesolimbic reward regions, we chose seed ROIs at group maxima for the right and left VTA and right NAcc. We transformed the seed ROI from Talairach to original space for within-subject analysis. We generated parametric maps of correlations with these seed ROIs for each individual as follows: to minimize spurious correlations due to artifactual fluctuations in-signal in the seed ROI, we used the trial onset as baseline for this analysis. We subtracted the intensity-normalized signal 1 s and 2 s prior to cue onset from the signal 5 s and 6 s after cue onset to estimate the percent signal change on each trial (for a similar approach, see Dolcos et al., 2004). We sorted trials by condition (Cue High Recognized, Cue High Forgotten, Cue Low Recognized, Cue Low Forgotten). Using these reduced data series at the seed ROIs as regressors of interest in AFNI 3dDeconvolve, we calculated the β coefficient and R^2 at each voxel in the imaged volume. Using AFNI 3dcalc, we calculated the correlation coefficient r for each condition, transformed the r values to Z scores, and contrasted pairs of conditions using $Z^* = |((z'1 - z'2)/(\mathrm{sqrt}((1/(n1-3)) + (1/(n2-3)))))|$, where n is the number of trials for conditions one and two. We averaged Talairach-transformed individual contrast maps using the meta-analytic formula described above. To test hypotheses about relationships between the hippocampus and the VTA seed ROI, we corrected for comparisons over the combined volume of the bilateral hippocampi (2098 mm^3). We chose voxel-wise thresholds that allowed separation of clusters within the hippocampus from surrounding activations ($p < 0.005$ for High versus Low and for High Recognized versus Low Recognized; $p < 0.01$ for High Recognized versus High Forgotten), and used AlphaSim (7 mm connection radius, 4 mm FWHM smoothing kernel, 1000 iterations) to determine the appropriate cluster threshold corresponding to an experiment-wise error rate of $p < 0.05$.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/50/3/507/DC1/.

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