Working Memory Maintenance Contributes to Long-term Memory Formation: Neural and Behavioral Evidence

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Abstract

■ Theories of human memory have led to conflicting views regarding the relationship between working memory (WM) maintenance and episodic long-term memory (LTM) formation. Here, we tested the prediction that WM maintenance operates in two stages, and that processing during the initial stage of WM maintenance promotes successful LTM formation. Results from a functional magnetic resonance imaging study showed that activity in the dorsolateral prefrontal cortex and hippocampus during the initial stage of WM maintenance was predictive of subsequent LTM performance. In a behavioral experiment, we demonstrated that interfering with processing during the initial stage of WM maintenance impaired LTM formation. These results demonstrate that processing during the initial stage of WM maintenance directly contributes to successful LTM formation, and that this effect is mediated by a network that includes the dorsolateral prefrontal cortex and the hippocampus. ■

INTRODUCTION

Episodic long-term memory (LTM) refers to processes supporting the formation and retrieval of memories for events, and working memory (WM) refers to processes that enable the maintenance and manipulation of information across brief periods of time. Although several studies have separately characterized the neural mechanisms of WM maintenance (D'Esposito & Postle, 2000) and LTM formation (Paller & Wagner, 2002), little is known about whether or how these memory processes interact. Hebb (1949) proposed that WM maintenance might be accomplished through reverberating activity in neural cell assemblies, and that this reverberating activity might serve to strengthen LTM traces for corresponding items. This assumption was later incorporated into formal models of memory (Atkinson & Shiffrin, 1968), generating the prediction that the amount of time spent actively maintaining an item should enhance LTM task performance. However, studies testing this prediction yielded inconclusive results (Nairne, 1983; Craik & Watkins, 1973; Woodward, Bjork, & Jongeward, 1973), leading some to suggest that WM maintenance and LTM formation might be functionally and neurally independent (Craik, 2002; Baddeley, 2000; Craik & Lockhart, 1972; Baddeley & Warrington, 1970; Shallice & Warrington, 1970).

Previous studies examining interactions between WM and LTM have generally treated WM maintenance as a unitary process. However, recent findings suggest that WM maintenance may operate in two stages (Johnson, Reeder, Raye, & Mitchell, 2002; Naveh-Benjamin & Jonides, 1984b). In the initial stage of WM maintenance, one must actively transform a sensory representation into an internal code that can be maintained in the absence of external stimulation, whereas in the late stage, maintenance of this code proceeds relatively automatically (Jolicoeur & Dell'Acqua, 1998; Naveh-Benjamin & Jonides, 1984a, 1984b). Processes related to the initial stage of WM maintenance have been described variously as "recoding" (Miller, 1956), "refreshing" (Johnson, Mitchell, Raye, & Greene, 2004; Johnson, Raye, Mitchell, Greene, & Anderson, 2003; Johnson, Reeder, et al., 2002; Raye, Johnson, Mitchell, Reeder, & Greene, 2002; Johnson, 1992), and "short-term consolidation" (Jolicoeur & Dell'Acqua, 1998).[1] Results from one study suggest that processing during the initial stage of WM maintenance disproportionately promotes successful LTM formation relative to the late stage of WM maintenance (Naveh-Benjamin & Jonides, 1984b). These findings suggest that distinguishing between early and late WM maintenance processes should allow for a more definitive assessment of the relationship between WM maintenance and LTM formation.

If, as Hebb (1949) proposed, neural activity during WM maintenance serves to strengthen LTM traces, we would expect sustained activity during the early or late

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stages of WM maintenance to be enhanced for items that are later remembered relative to items that are later forgotten. Furthermore, we would predict that disrupting the early or late stages of WM maintenance should impair LTM formation. Here, we tested these predictions in two experiments that required subjects to actively maintain novel visual objects across short memory delays. In Experiment 1, we used event-related functional magnetic resonance imaging (fMRI) to identify regions where activity early and late in the memory delay was predictive of subsequent LTM performance (Figure 1A). In Experiment 2, we performed a behavioral study to test whether interfering with processing early or late in the memory delay would impair LTM formation (Figure 1B).

Previous work has demonstrated that activity in the prefrontal cortex (PFC) and medial-temporal lobes (MTL) during memory encoding is predictive of successful LTM formation (Davachi, Mitchell, & Wagner, 2003; Ranganath, Yonelinas, et al., 2003; Otten, Henson, & Rugg, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998) and that these regions exhibit persistent activity during active maintenance of novel

Figure 1. Task design in Experiments 1 and 2. (A) Schematic depiction of the delayed recognition task used to elicit neural correlates of WM maintenance in Experiment 1. (B) Schematic depiction of the interference paradigm used to investigate the functional relationship between WM maintenance and LTM formation in Experiment 2.

information (Park et al., 2003; Davachi & Wagner, 2002; Ranganath & D'Esposito, 2001; Stern, Sherman, Kirch-hoff, & Hasselmo, 2001). Accordingly, we predicted that, in Experiment 1, PFC and MTL subregions should play a critical role in mediating effects of WM maintenance on LTM formation. We further predicted that disrupting WM processing in Experiment 2 would result in impaired LTM formation.
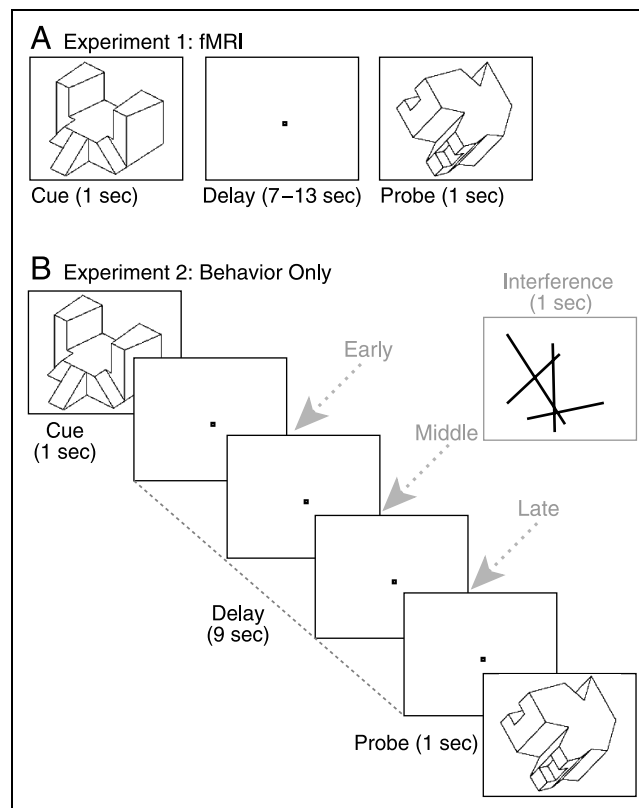
RESULTS

Experiment 1: Behavioral Results

In this experiment, subjects were scanned while performing a delayed recognition task with trial-unique line drawings of complex objects (Figure 1A). Accuracy on this task was high ($M = 92\%$, $SE = 0.8\%$). There were no significant differences in accuracy or reaction times (RTs) for trials as a function of probe type (match vs. nonmatch) [Accuracy: $t(14) = 1.58$, $p > .10$; RT: $t(14) < 1$] or delay length [Accuracy: $F(3,42) = 2.78$, $p = .09$; RT: $F(3,42) = 1.71$, $p > .15$].

Immediately after the scan session, subjects were given a surprise LTM test on objects presented during the scan. On this test, subjects saw a series of objects that were previously shown on WM trials as well as new foil objects. Subsequent LTM performance, assessed by postscan recognition confidence ratings, was high. Participants accurately recognized an average of 51.4% ($SD = 16.7\%$) of the previously encountered objects with high confidence ratings of "1" or "2." In contrast, only 10.7% ($SD = 5.4\%$) of foil objects were erroneously recognized with high confidence. The hit rate was significantly higher than the false alarm rate [$t(14) = 11.55$, $p < .001$]. LTM performance did not differ as a function of probe type [$t(14) = 1.44$, $p > .15$] or delay length [$F(3,42) < 1$]. Consequently, fMRI analyses of subsequent memory effects were performed collapsing across these variables.

Experiment 1: fMRI Results

Mapwise Analyses

Our first set of analyses identified areas generally engaged during WM maintenance, regardless of subsequent LTM performance. Based on the idea that processing might differ between early and late stages of WM maintenance (Johnson, Reeder, et al., 2002; Naveh-Benjamin & Jonides, 1984b), separate regressors modeled activity changes during the early and late stages of the memory delay (see Methods and Figure 7). As shown in Figure 2A, a vast network of cortical regions exhibited sustained activity increases during the early and late delay phases of the task. During the early delay period, activation was observed in bilateral superior parietal gyrus, left gyrus rectus (orbital PFC), left inferior temporal gyrus, and the left inferior occipital gyrus. In

Figure 2. Cortical and medial temporal activation related to WM maintenance and LTM formation. (A) Areas exhibiting overall activation changes during the early (top) and late (bottom) delay periods relative to the ITI. (B) Areas where activation during the early (top) and late (bottom) delay periods was significantly greater for subsequently remembered than for subsequently forgotten objects. Red boxes highlight regions in the left middle frontal gyrus and the left hippocampus where activity during the early delay period was predictive of subsequent LTM.
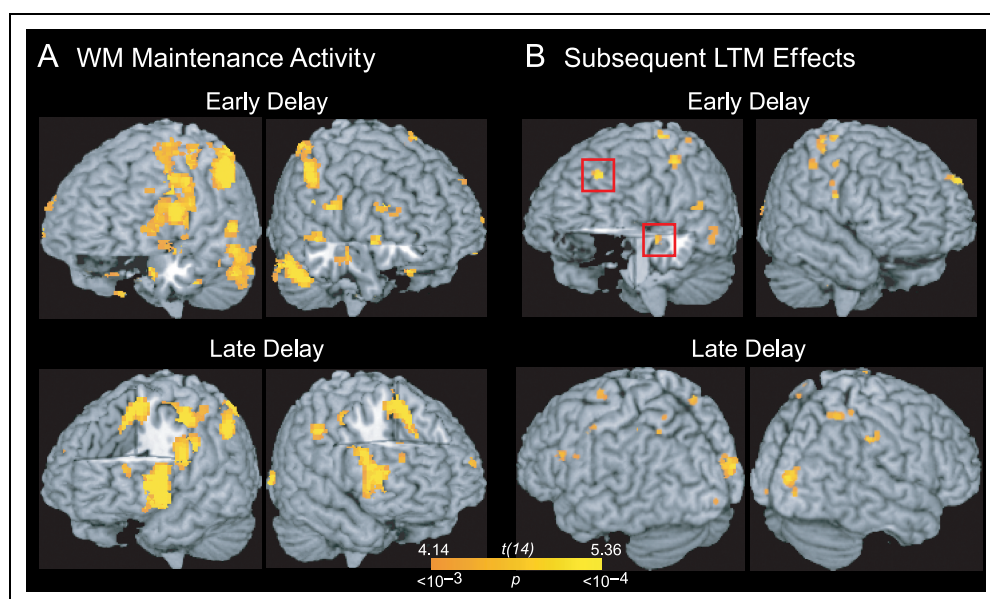
addition to these neocortical areas, the right hippocampus was recruited during the early delay period. These results replicate our previous findings showing hippocampal activation during WM tasks with novel stimuli (Ranganath & D'Esposito, 2001). During the late delay period, activation was observed in bilateral presupplementary motor area, frontal eye fields, dorsal cingulate, lingual, middle and superior occipital gyri, insula, and left middle temporal gyrus. In addition, bilateral regions in the inferior and middle frontal gyri and intraparietal sulcus were active during both the early and late stages of the memory delay. The topography of cortical regions showing delay-period activity corresponded well with regions identified in previous studies of visual WM maintenance (Curtis, Rao, & D'Esposito, 2004; Ranganath, Cohen, Dam, & D'Esposito, 2004; Linden et al., 2003; Munk et al., 2002; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002; Postle & D'Esposito, 1999; Courtney, Ungerleider, Keil, & Haxby, 1997). Example time courses of regions showing activation changes during the early or late delay relative to the intertrial interval (ITI) are shown in Figure 3. With the exception of the hippocampus, most areas identified in these contrasts responded robustly during each task phase (cue, early delay, late delay, and probe) for both remembered and forgotten items. Collectively, the results described above confirm that we were able to reliably identify areas that showed activity related to WM maintenance processes.

The next set of analyses identified areas where activity during different stages of the WM task was related to successful LTM formation. In these analyses, we identified regions where activity during the cue, early delay, or late delay periods on WM trials was greater for items that were subsequently remembered (endorsed with a "1" or "2" on the post-scan recognition confidence test) than for trials with novel items that were subsequently

forgotten (endorsed with a "5" or "6" on the postscan test). As in previous studies of LTM formation (Otten et al., 2001; Brewer et al., 1998; Wagner et al., 1998), we excluded items with midrange confidence ratings of 3 and 4 from these analyses in order to maximize our sensitivity to detect subsequent memory effects. By these criteria, the mean numbers of subsequently remembered and forgotten trials included in this contrast was trials were 29.07 (SD = 13.01) and 13.73 (SD = 8.40), respectively.

Regions exhibiting subsequent memory effects (i.e., significantly greater activation for items that were subsequently remembered than for items that were subsequently forgotten) during the cue, early delay, and late delay phases and example time courses for some of these regions are summarized in Table 1. Areas that exhibited enhanced activity for subsequently remembered items during the cue phase included the ventrolateral prefrontal (at or near Brodmann's area [BA] 44 and 45), orbital (BA 11) prefrontal, parahippocampal (BA 27), perirhinal (BA 36), and fusiform (BA 37) regions that have been identified in numerous previous studies of memory encoding (Davachi, Mitchell, et al., 2003; Ranganath, Yonelinas, et al., 2003; Davachi, Maril, & Wagner, 2001; Otten et al., 2001; Frey & Petrides, 2000, 2002; Brewer et al., 1998; Wagner et al., 1998). Transient increases in activity in each of these regions during initial processing of the cue stimulus influenced successful LTM formation.

Independent of the transient, stimulus-related effects described above, our experimental design allowed us to identify areas where activity during the early and late stages of WM maintenance was related to successful LTM formation. We specifically hypothesized that areas within the PFC and MTL would show subsequent memory effects during the delay period. Consistent with this
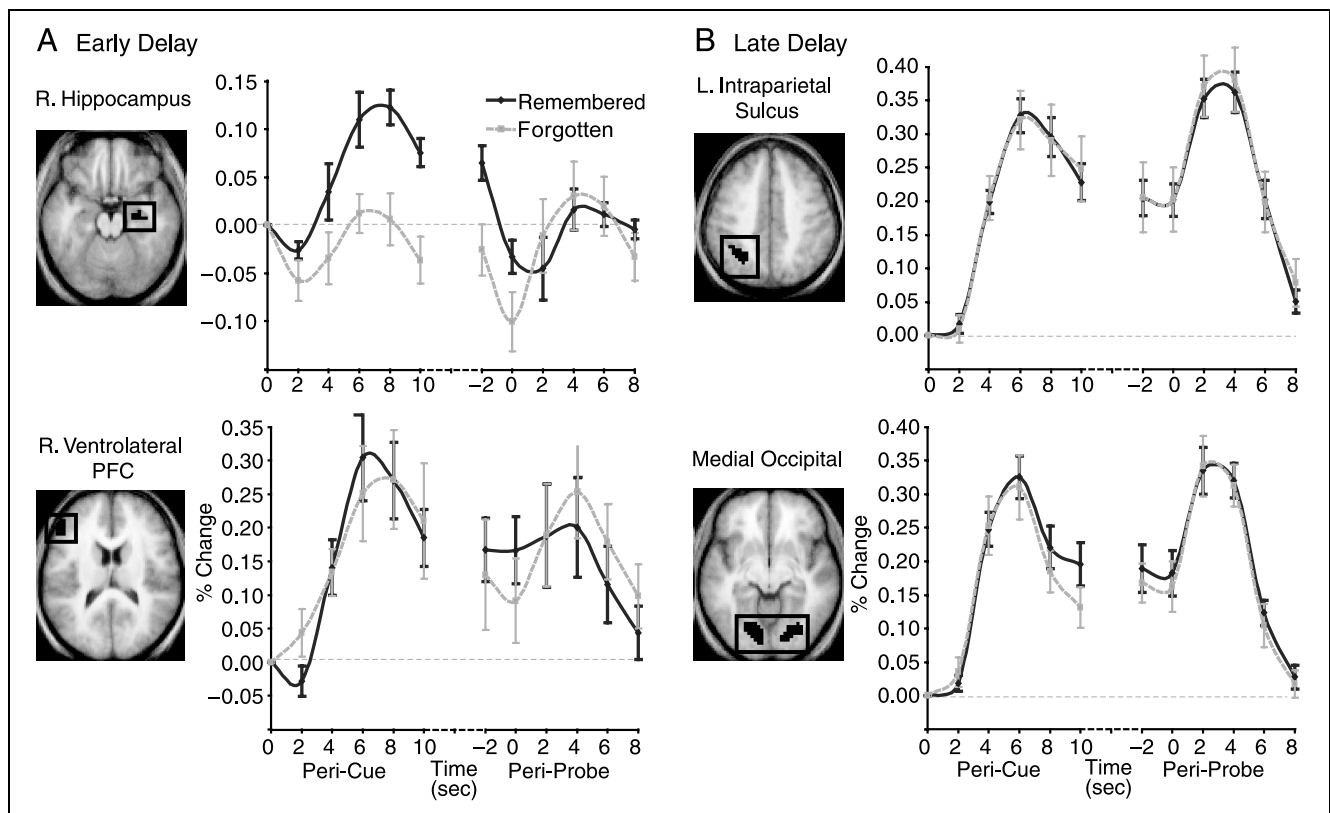
Figure 3. Temporal dynamics of activity related to WM maintenance. The time course of activity is shown for regions that exhibited increased activity during the early (A) and late (B) delay periods of each WM trial. Because the length of the memory delay varied from trial to trial, trial-averaged time courses were constructed by first realigning the time series for each trial separately to the onset of each cue and probe object. Each graph therefore shows percent signal change (x-axis) relative to trial onset as a function of time following cue or probe presentation. Early delay period activation in the right hippocampus (upper left) appeared to be driven entirely by subsequently remembered items and specific to the early delay period. However, activation in the ventrolateral PFC, intraparietal sulcus, and medial occipital cortex (as with other areas that exhibited overall increases in delay activity) was observed during each trial period and was similar for both remembered and forgotten trials.

prediction, activity in the left dorsolateral PFC (BA 9) and the left anterior hippocampus during the early delay period was enhanced for items that were subsequently remembered relative to items that were subsequently forgotten (Figures 2B and 4). In addition, visual, premotor, and motor areas were also identified in this contrast. During the late delay period, subsequent memory effects were primarily evident in posterior parietal and occipital cortical areas such as the intraparietal sulcus (BA 7/40), and the middle occipital gyrus (BA 18), as well as in the precentral gyrus (BA 6). The overall pattern of results suggests an anterior-to-posterior shift in subsequent memory effects observed between the early and late phases of the memory delay.

The results described above suggested that PFC and MTL activity during the early delay mediated interactions between WM maintenance and LTM formation. Given our a priori hypotheses regarding the PFC and MTL, we ran additional analyses to determine whether the magnitude of subsequent memory effects within the dorsolateral PFC and hippocampus was correlated with individual differences in memory performance (i.e., high confidence hit − false alarm rates). As shown in Figure 5,

we found that, within the hippocampus, the magnitude of the subsequent memory effect during the early delay period was significantly correlated with memory performance ($r = .54, p < .05$). These results suggest that hippocampal activity during the initial stage of WM maintenance was linked to successful LTM formation both within and across subjects.

Experiment 2

We interpreted the results of Experiment 1 as evidence that processing within the hippocampus and dorsolateral PFC during the initial stage of WM maintenance functionally contributed to successful LTM formation. Based on these results, we predicted that interfering with processing early in the memory delay should impair LTM formation. We tested this prediction in Experiment 2. As shown in Figure 1B, this behavioral study was similar to Experiment 1, except that, while performing the WM task, subjects were additionally instructed to perform a secondary task. Specifically, they were informed that, on most trials, an array of lines would be shown during the memory delay. When this happened,

Table 1. Local Maxima of Regions Exhibiting Subsequent LTM Effects during Cue or Delay Phases of Delayed Recognition Trials

Region	BA	x	y	z	k	t(14)
Cue Period						
R. Fusiform Gyrus	37	46	−49	−18	83	6.32
R. Middle Occipital Gyrus	19/37	32	−60	−7		5.48
R. Fusiform Gyrus	37	35	−46	−18		5.20
R. Thalamus		21	−24	0	8	6.30
R. Posterior Inferior Frontal Gyrus	44	46	7	32	35	5.87
R. Inferior Frontal Gyrus, Pars Triangularis	45	52	32	18	17	5.69
L. Inferior Frontal Gyrus, Pars Triangularis	45	−32	32	4	26	5.62
L. Gyrus Rectus	11	−24	35	−14		5.29
R. Gyrus Rectus	11	21	49	−18	14	5.52
L. Middle Occipital Gyrus	19/37	−24	−74	−10	85	5.10
L. Fusiform Gyrus	18	−38	−80	−14		5.00
L. Lingual Gyrus	19	−24	−66	0		5.00
R. Cuneus	17	14	−80	10	33	5.06
R. Middle Occipital Gyrus	19	46	−77	10		4.17
R. Middle Occipital Gyrus	39	42	−77	21	8	5.06
R. Middle Occipital Gyrus	18	28	−91	14	31	5.05
L. Posterior Collateral Sulcus (Parahippocampal Cortex)	37	−28	−42	−14	8	4.91
L. Middle Frontal Gyrus	9	−49	35	28	9	4.87
R. Inferior Temporal Gyrus	21	46	−60	0	7	4.82
L. Anterior Collateral Sulcus (Perirhinal Cortex)	36	−32	−21	−32	14	4.75
L. Anterior Collateral Sulcus (Perirhinal Cortex)	36	−32	−10	−35		4.70
L. Anterior Collateral Sulcus (Perirhinal Cortex)	36	−28	−14	−28		4.46
L. Intraparietal Sulcus	40	−32	−46	46	6	4.62
R. Inferior Occipital Gyrus	18	35	−77	−7	12	4.45
R. Inferior Occipital Gyrus	18	28	−84	−7		4.44
Early Delay Period						
R. Superior Occipital Gyrus	18	14	−98	14	28	6.95
R. Supplementary Motor Area	6	0	−4	56	22	6.55
L. Paracentral Lobule	6	−18	−28	66	24	6.21
L. Paracentral Lobule	5	−10	−42	67		4.51
L. Central Sulcus	4	−46	−18	46	9	6.16
L. Middle Frontal Gyrus	9	−32	46	35	10	5.51
R. Central Sulcus	2	28	−38	63	28	5.48
R. Central Sulcus	3	32	−35	56		4.86
R. Central Sulcus	4	24	−28	66		4.83
L. Anterior Hippocampus		−24	−14	−14	9	5.44
R. Cingulate Gyrus	24	14	−4	46	7	5.35

Table 1. (*continued*)

Region	BA	x	y	z	k	t(14)
L. Insula		−32	10	7	7	5.01
R. Cuneus	17	0	−84	7	11	4.93
L. Cerebellum		−18	−52	−24	12	4.72
Late Delay Period						
R. Middle Occipital Gyrus	18	24	−94	10	21	5.72
R. Lingual Gyrus	18	21	−88	−4		4.67
R. Supramarginal Gyrus	40	42	−35	38	6	5.03
L. Precentral Gyrus	4	−56	−14	52	9	5.02
R. Intraparietal Sulcus	7/40	32	−56	56	7	4.71

Abbreviations: R = right; L = left; BA = Brodmann's area; *k* = cluster size.

subjects were instructed to verbally indicate the number of lines shown in the array. The onset of the interference array was varied such that it was presented either early (1 sec), in the middle (4 sec), or late (7 sec) in the memory delay. On the remaining trials, no distracter was presented during the delay. After the WM task was completed, subjects were given a surprise LTM test on the previously rehearsed objects. With this design, we were able to analyze subsequent LTM performance as a function of the presence and temporal onset of interference with WM processing. The early delay interference probe was presented precisely at the time when we would expect subjects to be actively constructing internal representations of each object in WM (Jiang, 2004).[2] We therefore hypothesized that interference during the early stage of WM maintenance (i.e., early in the memory delay) should impair subsequent LTM performance.

We first examined the relationship between the timing of the distracter array and RT and accuracy on the match/nonmatch decision of each WM trial. Mean accuracy and RTs for each condition are shown in Table 2. Analyses of these data indicated that the timing of the interference probe did not significantly affect accuracy [$F(3,45) = 1.33$, $p > .20$], but did affect RTs [$F(3,45) = 8.20$, $p < .001$] on the match/nonmatch decision. Follow-up analyses showed that RTs were slower on late delay distracter and no-distracter trials than early delay or mid-delay distracter trials [all ts(15) > 2.9, all ps < .05]. These findings would suggest that there was no systematic relationship between the timing of the interference array and performance on the WM decision.

The next set of analyses concerned the critical question of whether there was a relationship between the timing of the distracter probe and performance on the subsequent LTM test. Results showed that the timing of the distracter probe significantly affected subsequent recognition performance [$F(3,45) = 4.71$, $p < .01$]. As

shown in Figure 6, LTM performance was significantly worse for items encountered on trials when the distracter array was presented early in the rehearsal period than for items encountered on trials when the distracter array was presented at other times or when no distracter was presented at all [all ts(15) > 2.7, all ps < .05]. Subsequent LTM performance for items encountered on trials when the distracter was presented in the middle of or late in the delay did not significantly differ, nor did LTM performance in these conditions differ from LTM performance for items encountered on no-distracter trials (all ts < 1). Collectively, these findings suggest that interfering with processing early in the delay period significantly and disproportionately impaired subsequent LTM performance, whereas interfering with processing later in the delay had no observable effect on subsequent LTM.

DISCUSSION

In the present study, we sought to characterize the relationship between different stages of WM maintenance and LTM formation. Results of Experiment 1 showed that activity in the dorsolateral PFC, hippocampus, and other regions during the early stage of WM maintenance was predictive of subsequent LTM. Results of Experiment 2 showed that processing during the early stage of WM maintenance disproportionately influenced LTM formation over and above processing implemented during the cue period or processing later in the memory delay.

### Prefrontal Contributions to WM Maintenance and LTM Formation

Results from neuropsychological studies suggest that damage to the PFC can disrupt performance on WM and LTM tasks that demand executive control (Ranganath
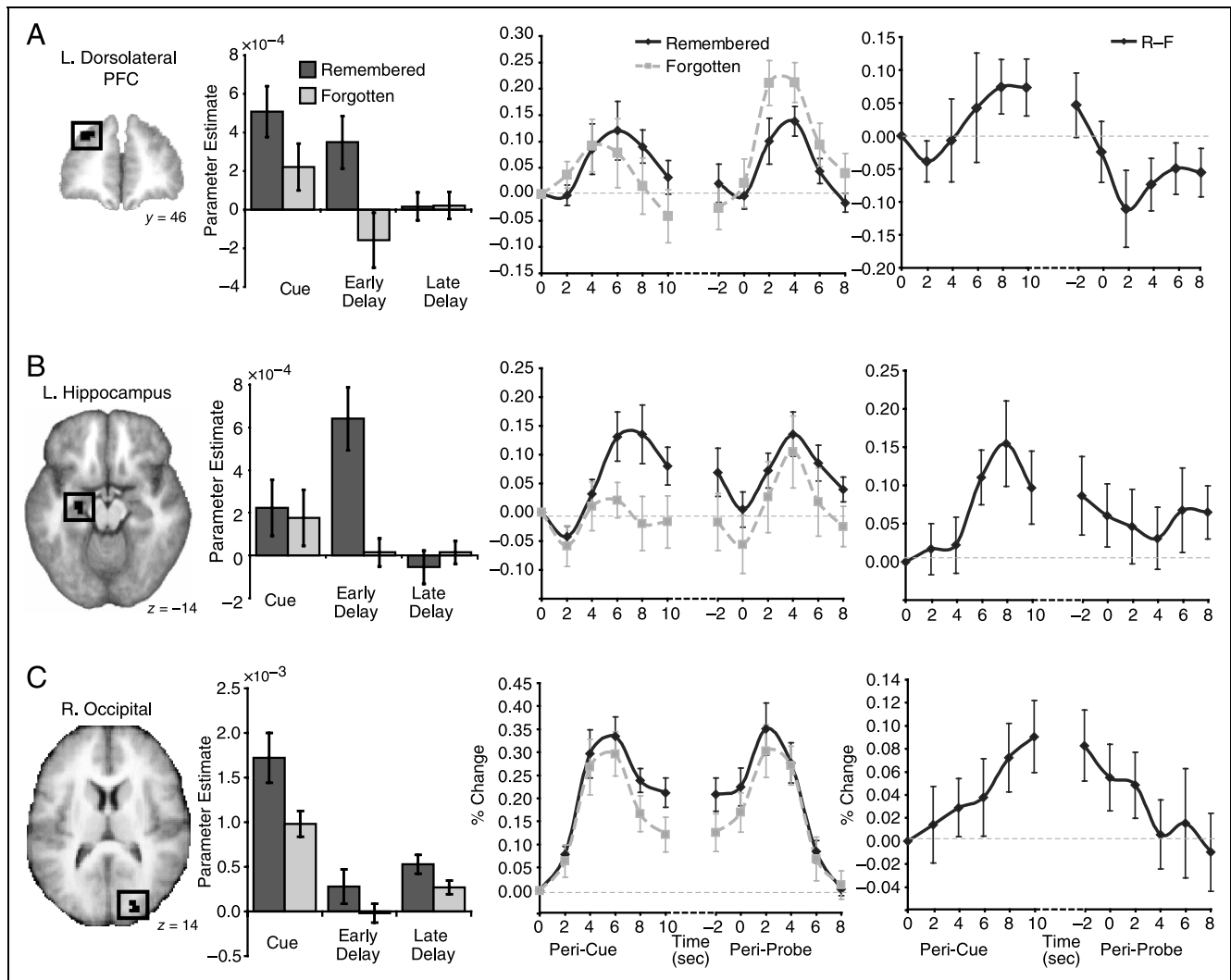
Figure 4. Neural activity during WM maintenance that was predictive of subsequent LTM. Data are shown for regions in (A) the left dorsolateral PFC (BA 9) and (B) in the left hippocampus that showed subsequent memory effects during the early delay period, and (C) for a region in the right occipital cortex (BA 18) that showed a subsequent memory effect during the late delay. Left: Parameter estimates indexing estimated response amplitudes during the cue, early delay, and late delay phases of WM trials are plotted for each of region. Center: Trial-averaged time courses are plotted for subsequently remembered and forgotten items. Right: The time course of the difference in activity between subsequently remembered and forgotten items.

& Knight, 2003; Shimamura, 2000; D'Esposito & Postle, 1999). Within the PFC, results from previous neuro-imaging studies would suggest that ventrolateral sub-regions (BA 44, 45, and 47) should have been the most likely sites of interaction between WM maintenance and LTM encoding processes—ventrolateral PFC activation is routinely reported in studies of WM maintenance (Ranganath, Cohen, et al., 2004; Ranganath, Johnson, & D'Esposito, 2003; Pessoa et al., 2002; Postle & D'Esposito, 1999; Courtney et al., 1997) and LTM for-mation (Davachi, Mitchell, et al., 2003; Ranganath, Yonelinas, et al., 2003; Otten et al., 2001; Henson et al., 1999; Brewer et al., 1998; Wagner et al., 1998). These findings have prompted many researchers to sug-gest that ventrolateral prefrontal regions may promote successful LTM formation through their roles in WM
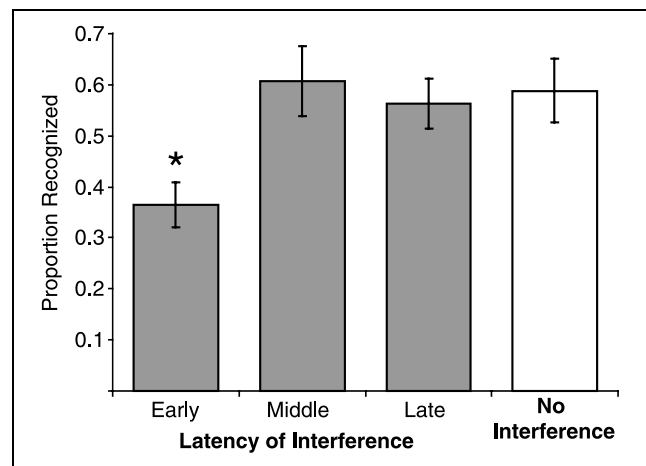
processes that bias the selection and maintenance of relevant item features (Buckner, 2003; Ranganath & Knight, 2003; Fernandez & Tendolkar, 2001; Wagner, 1999). Our results were partly consistent with this view, in that the ventrolateral PFC (BA 44, 45, and 47) exhib-ited sustained activity when subjects were engaged in active WM maintenance (Figure 2), and that activity in some of these regions (BA 44 and 45) was predictive of subsequent LTM performance (Table 1). However, the magnitude of ventrolateral PFC activity was specifically related to subsequent LTM performance during initial processing of each object (i.e., during the cue period), rather than during WM maintenance. A similar pattern of results was observed in the orbital PFC (BA 11), another PFC subregion implicated in LTM formation (Ranganath, Yonelinas, et al., 2003; Frey & Petrides, 2000, 2002). Thus,
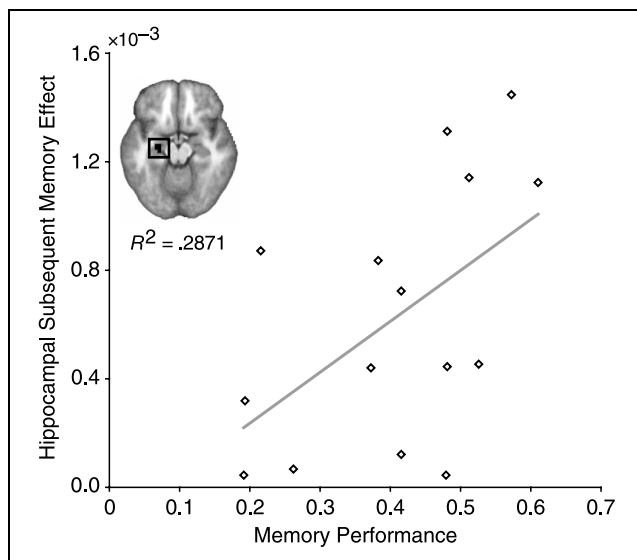
Figure 5. Hippocampal recruitment during the early delay predicted individual differences in memory performance. A scatterplot shows the relationship between subsequent memory effects (i.e., the difference in early delay parameter estimates between subsequently remembered and subsequently forgotten trials) observed in the left hippocampus and performance on the LTM test (i.e., the difference between the proportion of high confidence hits and high confidence false alarms). These data demonstrate that hippocampal activity during the initial stage of WM maintenance was strongly predictive of successful LTM formation both within and across subjects.

Figure 6. Interfering with the early stage of WM maintenance significantly and disproportionately impaired LTM formation. Results from Experiment 2 are plotted, showing the proportion of objects subsequently recognized with high confidence as a function of the latency of presentation of the distracter array. Subsequent LTM was significantly worse on trials when the interference array was presented early in the memory delay relative to other trial types, which did not differ from one another.
*Represents substandard conditions during the experiment.

the ventrolateral and orbital PFC might initially focus processing of items in a manner that enhances the distinctiveness or strength of a memory trace, but further activity in these regions during WM maintenance does not necessarily result in substantial LTM enhancement.

In contrast to ventrolateral PFC activation, dorsolateral PFC activation has been observed only infrequently in event-related fMRI studies of LTM encoding (Savage et al., 2001; Fletcher, Shallice, & Dolan, 1998). Three studies have even reported *decreases* in dorsolateral PFC activation for remembered items (Dasselar, Prince, & Cabeza, 2004; Otten & Rugg, 2001; Wagner & Davachi, 2001). The lack of extensive dorsolateral PFC activation in previous neuroimaging studies is surprising, given that evidence from lesion (Duarte, Ranganath, & Knight, 2004; Gershberg & Shimamura, 1995) and transcranial magnetic stimulation (Kohler, Paus, Buckner, & Milner, 2004; Rami et al., 2003; Sandrini, Cappa, Rossi, Rossini, &

Miniussi, 2003; Epstein, Sekino, Yamaguchi, Kamiya, & Ueno, 2002; Rossi et al., 2001) studies suggest a potentially important role for this region in promoting LTM formation. However, except for one study (Davachi, Maril, et al., 2001), previous neuroimaging studies of LTM formation have not required active WM maintenance. Our results suggest that the dorsolateral PFC (BA 9) was recruited during the initial stage of WM maintenance (Figure 4). This finding is consistent with results from a single-unit recording study in which the temporal characteristics of dorsolateral PFC activity were examined during a spatial WM task (Kojima & Goldman-Rakic, 1982). Critically, these investigators found that over half of the neurons that exhibited persistent delay-period activity exhibited maximal activity during the initial few seconds of the delay period.

Our results also converge with an emerging pattern in neuroimaging studies of WM. For example, Johnson, Mitchell, et al. (2004), Johnson, Raye, et al. (2003), and Raye et al. (2002) have observed reliable increases in dorsolateral PFC (left BA 9) activation when subjects attempted to ''refresh'' a recently activated representa-

Table 2. Mean Accuracy and Reaction Time (RT) for WM decisions in Experiment 2

	Latency of Interference			
	Early	*Middle*	*Late*	*No Interference*
Accuracy	0.902 (0.108)	0.928 (0.079)	0.944 (0.047)	0.949 (0.072)
RT (msec)	879.9 (252.83)	860.8 (187.70)	971.5 (188.58)	1022.8 (276.22)

Note: SD values are in parentheses.

tion. In a similar vein, Bor, Cumming, Scott, and Owen (2004) and Bor, Duncan, Wiseman, and Owen (2003) reported increased dorsolateral PFC activation during WM tasks in which sequences of digits or locations could be "chunked" relative to tasks in which sequences of digits or locations were unstructured and hence difficult to chunk. Finally, Prabhakaran, Narayanan, Zhao, and Gabrieli (2000) reported enhanced dorsolateral PFC activation during a task that required subjects to bind different kinds of information in WM. Collectively, each of these results suggest that the dorsolateral PFC plays an important and previously underappreciated role in processing during the initial stage of WM maintenance, which in turn contributes to successful LTM formation (see below).

MTL Contributions to WM Maintenance and LTM Formation

Although the hippocampus, parahippocampal cortex, and perirhinal cortex are traditionally thought to contribute solely to LTM, substantial evidence suggests that these regions may contribute to both WM and LTM. For example, lesion studies in humans and monkeys suggest that large MTL lesions that include the perirhinal cortex have devastating effects on memory for novel visual objects, even across short delays spanning a few seconds (Buffalo, Reber, & Squire, 1998; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Eacott, Gaffan, & Murray, 1994; Suzuki, Zola-Morgan, Squire, & Amaral, 1993; Murray & Mishkin, 1986; Zola-Morgan & Squire, 1985). Furthermore, neurophysiological studies have found robust correlates of WM maintenance within the entorhinal and perirhinal cortices (Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002; Suzuki, Miller, & Desimone, 1997; Nakamura & Kubota, 1995, 1996; Miyashita & Chang, 1988), and several recent fMRI studies have reported hippocampal activity associated with WM for novel stimuli (Park et al., 2003; Cabeza, Dolcos, Graham, & Nyberg, 2002; Davachi & Wagner, 2002; Ranganath & D'Esposito, 2001; Stern et al., 2001).

In the present study, we found that recruitment of the anterior hippocampus during the initial stage of WM maintenance was directly related to successful LTM formation. The prolonged latency (during the early delay period) and sustained time course of this activity (Figure 4B) was qualitatively different from those of hemodynamic responses reported in studies of LTM formation that did not require active maintenance (Reber et al., 2002; Kirchhoff, Wagner, Maril, & Stern, 2000). These findings suggest that the hippocampus is a key site for interactions between WM and LTM.

One might argue that delay-period activity in the hippocampus might reflect incidental processing that was not related to WM maintenance. For example, during the delay period, subjects might have attempted to compare active information in WM to recently formed LTM representations, which in turn might have driven hippocampal activity for remembered items. However, results from Experiment 2 showed that disrupting processing during the initial portion of the memory delay impaired LTM. If hippocampal activity solely reflected a comparison between information in WM and LTM, it is unclear why interfering with this process would result in impaired LTM. More generally, available evidence suggests that when subjects are required to actively maintain complex, novel information, hippocampal activity increases well beyond levels seen in tasks that simply involve intentional encoding of these items. For example, in a previous study (Ranganath & D'Esposito, 2001), we found that the anterior hippocampus exhibited robust delay-period activity in a WM task using novel face stimuli, but the same region exhibited no reliable signal changes during a task that required intentional encoding of faces in anticipation of a subsequent LTM test (Ranganath & D'Esposito, 2001). This pattern of results suggests that the demand to actively maintain a complex, novel stimulus results in significantly increased hippocampal recruitment above and beyond activity that is elicited by initial stimulus encoding.

The results of the present study complement our previous results (Ranganath & D'Esposito, 2001) by demonstrating that hippocampal activity during WM maintenance is correlated with successful LTM formation. This correlation could be interpreted in at least two ways. One possible explanation is that, during the early delay period, subjects' attempts to construct an internal representation of each object resulted in additional input to the hippocampus, which resulted in increased activity for items that were successfully encoded into LTM. By this view, hippocampal activity in this and other studies of WM for novel items (Park et al., 2003; Davachi & Wagner, 2002; Ranganath & D'Esposito, 2001; Stern et al., 2001) reflects the incidental enhancement of LTM encoding produced by WM maintenance, rather than direct involvement of this region in WM processes. An alternate way of explaining the same finding is that the hippocampus contributes to WM maintenance by virtue of its role in LTM (Ranganath & D'Esposito, 2001). Specifically, we suggest that novel object representations were initially encoded in the MTL, and that these representations were used to reconstruct and maintain the pattern of activity corresponding to these objects in posterior cortical areas later in the delay. By this view, the hippocampus plays a critical role in LTM formation, and sustained activation of these new LTM traces additionally facilitates reconstruction of complex, novel information in WM. Distinguishing between these views will be difficult, but future studies could address this issue through careful examination of WM in patients with focal MTL damage (Hannula, Cohen, & Tranel, 2003). In addition, event-related analyses of functional connectivity (Rissman, Gazzaley, & D'Esposito, 2004) between MTL and posterior cortical regions during the

performance of WM tasks can provide another source of evidence to determine whether, as we suggest, the hippocampus plays a role in dynamic reconstruction of complex, novel information in WM.

Subsequent Memory Effects in Posterior Cortical Areas

Although our a priori hypotheses concerned PFC and MTL regions, we noted that several posterior cortical areas also exhibited large and reliable subsequent memory effects during the memory delay. Some of these effects, such as those observed in motor cortical areas, are difficult to interpret, but might merit additional consideration, given that they have been observed in some other studies of LTM encoding (e.g., Ranganath, Yonelinas, et al., 2003; Buckner, Wheeler, & Sheridan, 2001; Otten et al., 2001). One somewhat surprising finding was that extensive regions of the occipital cortex exhibited persistent activity increases during the memory delay, and that this activity was correlated with successful LTM formation during both the early and late delay periods. This pattern of results suggests that visual WM maintenance and its effects on LTM formation might be mediated in part through persistent activity in the early visual cortex (Gisiger, Kerszberg, & Changeux, 2004; Hebb, 1949). Interestingly, this interpretation is consistent with the fact that our visual distracter in Experiment 2 impaired LTM formation. Future work would be necessary to confirm that such distraction effects are specific to visual stimuli, as we might expect if plasticity in visual cortex contributed to object LTM formation.

Functional Relationship between WM Maintenance and LTM Formation

As noted earlier, the relationship between WM maintenance and LTM formation has been an issue of considerable debate. Although it is clear that processing that emphasizes formation of associations across multiple items ("elaborative rehearsal") strongly influences LTM formation (Craik, 2002; Hunt & Einstein, 1981; Craik & Lockhart, 1972), the role of WM maintenance in new LTM formation has been strongly disputed. Much of the dispute in the literature has been over whether there is a continuous relationship between the amount of uninterrupted rehearsal time and subsequent LTM performance. Results from Experiments 1 and 2 address this issue by demonstrating that there is a relationship between WM and LTM, but that this relationship is clearly not linear. In Experiment 1, we found no significant relationship between the length of the delay on WM trials and subsequent LTM performance. Furthermore, results from Experiment 2 showed that LTM performance was impaired when an interference array

was presented early in the delay, but not if it was presented in the middle or the late phases of the memory delay (Figure 6). These data suggest a real link between WM processing and LTM formation, but they are also inconsistent with the idea that more time spent engaging in WM maintenance simply results in better memory.

One might question whether the results that we obtained might be peculiar to the complex visual stimuli used in this experiment. Indeed, it is possible that the novelty and complexity of these objects necessitated specific processing during WM maintenance that might not be necessary for rehearsing simple, overlearned information. Relevant to this question, two studies (Naveh-Benjamin & Jonides, 1984a, 1984b) showed that increasing the number of times a word was rehearsed from 1 to 4 or 5 times significantly increased the likelihood that it would be subsequently remembered, but further increasing the number of rehearsals to 10 did not result in additional improvements in subsequent LTM performance. These findings suggest that, to some degree, the type of nonlinear relationship between WM processing and LTM formation observed here might apply even in the case of simple overlearned stimuli such as verbal material.

The present behavioral and imaging results are open to at least two interpretations that can be tested in future studies. Our interpretation is that, under at least some circumstances, processing qualitatively differs between the early and late stages of WM maintenance, and that early WM maintenance processes disproportionately contribute to LTM formation. An alternate explanation is that WM maintenance is more or less a unitary process, but for reasons that are presently unclear, only the initial few seconds of maintenance processing actually contribute to LTM formation. If, as we and others have suggested, early WM processing is relatively effortful and late WM processing is relatively automatic, then these two explanations could be contrasted in behavioral studies using methods to characterize the degree to which controlled processing is engaged during different stages of WM maintenance. This issue was examined in studies of verbal WM by Naveh-Benjamin and Jonides (1984b), who showed in three experiments that the first four rehearsals of a word engaged much more controlled processing than subsequent rehearsals. These results suggest that, at least under some circumstances, processing during early and late stages of WM maintenance can be qualitatively distinguished. Further work examining the temporal dynamics of controlled processing during WM maintenance will be necessary to examine the generalizability of their findings across other stimuli and task situations.

Finally, we note that an interesting aspect of the present results is that, although presentation of an interference probe during the early delay disrupted subsequent LTM performance, it had no reliable effect on WM task performance (Table 2). Nonetheless, this

should not be taken to suggest that the distracter task did not have any effect on WM processing. Indeed, it is likely that the interference manipulation affected the ability to form and maintain holistic, detailed object representations but did not affect maintenance of low-level visual features (e.g., a triangle on the lower right corner of the object). Whereas maintenance of low-level featural representations might be sufficient to make a WM decision, overlap of these features across successive objects would make them insufficient to support accurate LTM performance. Accordingly, it is reasonable to suggest that our interference manipulation affected the overall quality of the WM representation, but did not eliminate the ability to maintain features that could be used to make decisions on the WM task.

Conclusions

By functionally dissociating early and late WM maintenance processing, the present results call into question common assumptions that underlie the overwhelming majority of neuroscientific investigations of WM tasks. For example, most neurophysiological (O'Scalaidhe, Wilson, & Goldman-Rakic, 1997; Suzuki et al., 1997; Nakamura & Kubota, 1995; Miller, Li, & Desimone, 1993; Fuster, 1990; Miyashita & Chang, 1988) and neuroimaging studies of object WM (Ranganath, Cohen, et al., 2004; Ranganath, DeGutis, & D'Esposito, 2004; Ranganath, Johnson, et al., 2003; Linden et al., 2003; Jha & McCarthy, 2000; Courtney et al., 1997) have used delay tasks similar to those used here. In such studies, sustained neural responses observed during the memory delay are typically interpreted to reflect neural correlates of a unitary WM maintenance process (Curtis & D'Esposito, 2003). Our results suggest that, in fact, the processes supporting the early and late stages of WM maintenance might be quite different. More specifically, our results suggest that the early stage of WM maintenance contributes to successful LTM formation, and that this effect is mediated by a network that includes the dorsolateral PFC and the hippocampus.

METHODS

Experiment 1

Participants

Fifteen (8 men; aged 20–28) participants were recruited from the UC Davis student community. Participants gave informed consent prior to the experiment and were paid for their participation.

Behavioral Procedure

The materials used in this study were line-drawings of novel "possible" objects (see Figure 1) drawn from previous studies (Williams & Tarr, 1997, 1999; Schacter

& Cooper, 1993; Schacter, Cooper, & Valdiserri, 1992; Schacter, Cooper, & Delaney, 1990). Prior to the scanning session, participants were trained to learn eight of these objects ("learned" objects) by performing 48 trials of an immediate match-to-sample task. Participants also performed eight delayed-recognition trials using these stimuli to ensure that they were comfortable with the task.

During the scanning phase, participants first performed a visuomotor response task, the results of which were used to empirically estimate a subject-specific hemodynamic response function (HRF; see below). Next, participants performed 128 trials of a delayed-recognition task. On each trial, a cue object was shown for 1 sec, and subjects were instructed to maintain a vivid mental image of the stimulus across a variable 7–13 sec delay period. Following the delay, a probe object (either a matching or nonmatching object) was shown for 1 sec, and participants pressed one of two buttons on a response box to indicate whether or not the probe matched the cue stimulus. Match/nonmatch decisions were made by pressing one of two buttons on a magnet-compatible response device. A variable 9–15 sec ITI preceded the start of the next trial. Half of the trials contained items seen in the prescan training session ("learned"; 8 presentations of each item) and half contained novel, trial-unique items (i.e., items that were not presented during the prescan training session). There were an equal number of match and nonmatch trials, and all trial types were presented in a pseudorandom order. Results from the trials with learned stimuli will not be discussed here.

Following the scanning session, participants were given a surprise recognition memory test to assess LTM for all of the items that were shown as cue stimuli in the scanner (64 novel and 8 learned plus 37 novel foils). In this test, participants were shown each item individually on a computer screen and were instructed to rate each item on a confidence scale that ranged from 1 ("definitely seen during scanning phase") to 6 ("definitely NOT seen during scanning phase"). Subjects were instructed to distribute their responses across the entire range of the scale when making their decisions.

MRI Acquisition and Processing

MRI data were collected on a 1.5-T GE Signa scanner at the UC Davis Research Imaging Center. Functional imaging was done with a gradient-echo echo-planar imaging (EPI) sequence (TR = 2000, TE = 40, FOV = 220, 64 × 64 matrix, voxel size = 3.4375 × 3.4375 × 5 mm), with each volume consisting of 24 axial slices. Co-planar and high-resolution T1-weighted images were also acquired. fMRI data preprocessing was performed with Statistical Parametric Mapping (SPM99) software for all subjects. EPI images were sinc interpolated in time to correct for between-slice timing differences in image

acquisition, realigned using a six-parameter, rigid-body transformation algorithm, spatially normalized to the template from the International Consortium for Brain Mapping Project (Cocosco, Kollokian, Kwan, & Evans, 1997), resliced into 3.5-mm isotropic voxels, and spatially smoothed with an 8-mm FWHM Gaussian filter.

MRI Data Analysis

Activity changes during each phase of each trial were deconvolved using multiple regression (Curtis et al., 2004; Ranganath, Cohen, et al., 2004; Munk et al., 2002; Sakai, Rowe, & Passingham, 2002; Ranganath & D'Esposito, 2001; Postle, Zarahn, & D'Esposito, 2000; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Courtney et al., 1997; Zarahn, Aguirre, & D'Esposito, 1997). The basic assumption behind this approach is that the time course of BOLD signal changes on any given WM trial can be considered as distinct patterns of neural activity that are convolved with the HRF. Covariates modeling BOLD signal changes associated with the cue, early delay, late delay, and probe periods of each trial were constructed by convolving vectors of expected neural activity associated with each of these components with a subject-specific HRF estimated from responses in the central sulcus during the visuomotor response task (Handwerker, Ollinger, & D'Esposito, 2004; Ranganath, Cohen, et al., 2004; Aguirre, Zarahn, & D'Esposito, 1998). Data from the visuomotor response task were not available for one subject, and for this subject, covariates were constructed by convolving the vector of expected neural activity with the "canonical" HRF included in SPM99.

The vectors of expected neural activity associated with each task component for trials of different delay lengths are shown in Figure 7. The construction of the early and late delay covariates was based on the assumption that processing associated with the initial stage of WM maintenance would occur during the first few seconds of the delay, regardless of the overall delay length. In contrast, we assumed that processing associated with the second stage of WM maintenance would persist throughout the remainder of the memory delay (see Jiang, 2004, for theoretical justification for these assumptions; Raye et al., 2002; Naveh-Benjamin & Jonides, 1984a, 1984b).

As shown in Figure 7, the onset and offset of delay-period vectors were spaced apart from the cue and probe period vectors so as to minimize the possibility that neural activity limited to the cue and probe periods would load on the early or late delay covariates (Ranganath & D'Esposito, 2001; Postle et al., 2000; Zarahn et al., 1997). Because the length of the delay period varied from trial to trial, our design allowed us to effectively deconvolve late delay responses from early delay and probe responses (Sakai & Passingham, 2003; Sakai et al., 2002; Rowe et al., 2000). Inspection of ob-
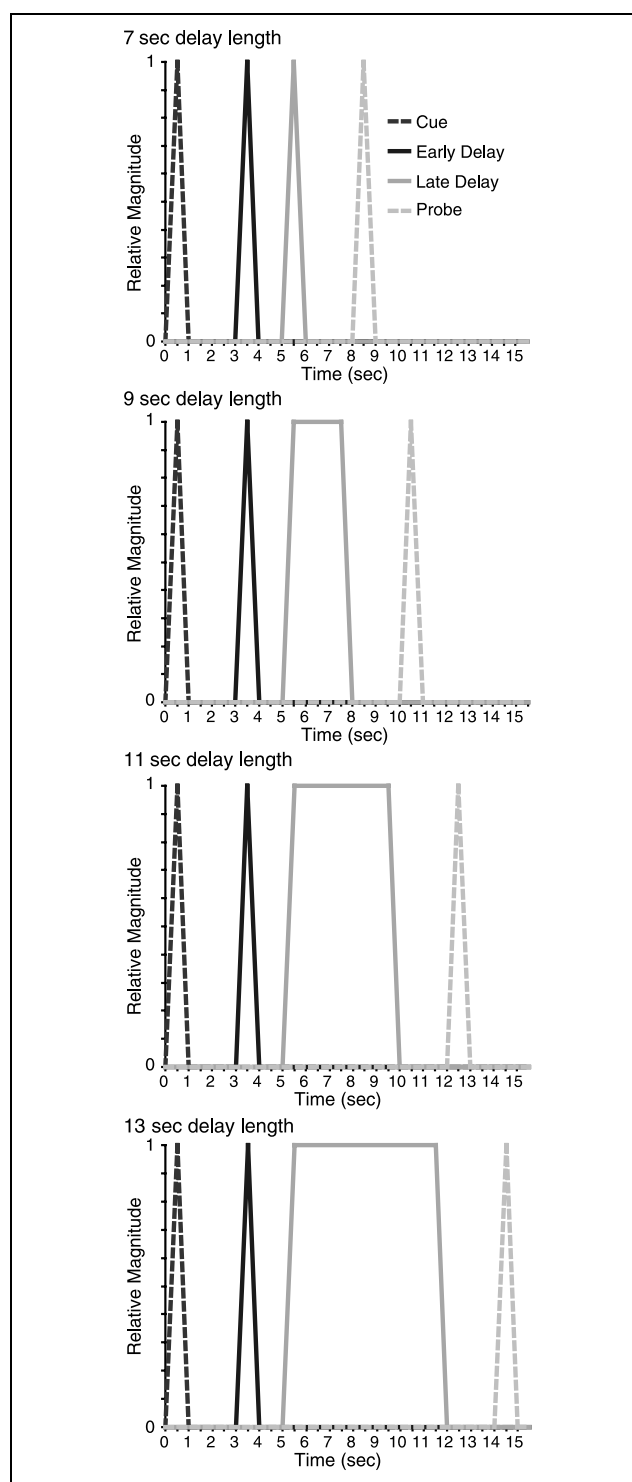
Figure 7. Vectors of expected neural activity corresponding to cue, early delay, late delay, and probe phases are shown separately for trials of different delay lengths (7–13 sec). Covariates modeling BOLD responses on each WM trial were constructed by convolving these neural activity vectors with subject-specific HRFs.

served activity time courses (see Figure 4) suggests that the model estimates accurately characterized the data.

Responses during each task phase were modeled separately for trials with learned stimuli, trials with novel

stimuli that were subsequently remembered with high confidence (items that were endorsed with a "1" or "2" confidence rating on the postscan LTM test), trials with novel stimuli that were subsequently recognized with low confidence (items that were endorsed with a "3" or "4" confidence rating), and trials with stimuli that were subsequently forgotten (novel items that were endorsed with a "5" or "6" on the postscan LTM test). These covariates only modeled responses for trials that were associated with correct match/nonmatch decisions on the WM probe. Trials associated with incorrect WM decisions were modeled with separate covariates. Additional nuisance covariates modeled global signal changes that could not be accounted for by variables in the design matrix (Desjardins, Kiehl, & Liddle, 2001), trial-specific baseline shifts, and an intercept. The convolution matrix included a time-domain representation of the $1/f$ power structure (Aguirre et al., 1998; Zarahn et al., 1997) and filters to remove frequencies above 0.25 Hz and below 0.02 Hz.

Following single-subject analyses, images of parameter estimates for each contrast of interest (i.e., linear combinations of regression coefficients from the GLM) were entered into a second-level one-sample t test, in which the mean estimate across participants at each voxel was tested against zero. Significant regions of activation were identified using an uncorrected two-tailed threshold of $p < .001$ and a minimum cluster size of at least 6 contiguous voxels. For visualization purposes, thresholded statistical parametric maps were overlaid on T1-weighted images using MRIcro software (Rorden & Brett, 2000). Further analyses were performed on regions of interest, which were defined by selecting all contiguous, significantly active voxels in anatomically constrained areas at a two-tailed threshold of $p < .001$.

Experiment 2

The materials and methods used in this behavior-only experiment were similar to Experiment 1, but with the following modifications. As shown in Figure 1B, subjects performed a delayed recognition task in which a cue object was presented for 1 sec, followed by a 9-sec delay, followed by a probe object for 1 sec. Subjects were instructed to maintain a vivid mental image of each object during the delay in anticipation of the upcoming test probe. On 75% of the trials, an array of overlapping lines (3, 4, or 5 lines in one of three different configurations) was briefly presented for 1 sec at some point during the delay. When an array was presented, subjects were instructed to verbally report the number of lines in the interference array, and these responses were recorded by an experimenter. Across trials, the onset latency of the interference array was varied such that it was equally likely to appear early (1 sec), in the middle

(4 sec), or late (7 sec) in the delay period. On the remaining 25% of the trials, no interference was presented.

Following completion of 60 WM trials, subjects were given a surprise LTM test with 60 real items and 60 foil objects. As in Experiment 1, subjects made recognition confidence judgments on a 1–6 scale, and the dependent measure was the proportion of trials recognized with high confidence ("1" or "2" responses). In this experiment, analyses of the relation between the timing of the interference probe and subsequent LTM performance only included trials with nonmatching probes that were associated with correct WM decisions. Trials with matching probes were not included in subsequent memory analyses, because on these trials, processing of the matching probe stimulus would defeat the purpose of interfering with WM maintenance (i.e., processing the probe stimulus would allow subjects to refresh a mental representation of the cue stimulus). Nonetheless, the reported pattern of results was unchanged if results from match and nonmatch trials were included in this analysis.

Notes

1. We note that these processes (particularly short-term consolidation) are sometimes described as WM "encoding" processes, particularly in studies with simple overlearned verbal or spatial stimuli, where initial WM processing can be rapid and transient (Vogel & Luck, 2002; Jolicoeur & Dell'Acqua, 1998). The use of the term "encoding" in this context refers to the processing of an item such that it can be actively maintained. In our experiment, it is likely that subjects' attempts to construct an internal representation of each object extended several seconds into the memory delay, and therefore this processing would be more aptly described as a stage of maintenance, rather than encoding. Our terminology has the added advantage of clearly distinguishing WM-related processing from other types of stimulus-driven perceptual processing that are sometimes described by the term "encoding."

2. It could be argued that the operationalization of "early delay" differed between Experiments 1 and 2. The onset of the covariate modeling early delay activity in Experiment 1 was

timed 2 sec after the onset of the memory delay. In contrast, the onset of the early delay interference probe in Experiment 2 was timed 1 sec after the onset of the memory delay. Available evidence from behavioral studies suggests that initial WM maintenance processing probably occurs soon after initial processing of the cue item and that it could persist at least 1–3 sec into the memory delay. After that, we would expect maintenance-related activity to be well established in the posterior cortex and require much less top-down input. This is why, in Experiment 2, we targeted 1 sec as the "early delay" period to interfere with. In Experiment 1, however, we faced a problem inherent in fMRI—the sluggishness of the BOLD response makes it difficult to deconvolve sequential neural events that occur close together in time. We therefore timed the onset of the early delay covariate to best model activity specific to the initial stage of WM maintenance. It is possible that the early delay covariate might have underestimated the number of brain regions mediating the relationship between initial WM maintenance and successful LTM formation. However, this concern does not affect interpretation of the significant results related to the early delay covariate.

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