

ORIGINAL ARTICLE

Expectations of Task Demands Dissociate Working Memory and Long-Term Memory Systems

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Abstract

Many aspects of the complex relationship between working memory (WM) and long-term memory (LTM) remain unclear. Here, we manipulated task demands on a brief delayed-recognition paradigm to reveal behavioral and neural dissociations between these systems. Variations from a Baseline task included 3 challenges: increased delay duration, distraction during maintenance, and more closely matched memory probes, which were presented in behavioral experiments and during functional magnetic resonance imaging. Each of the challenges resulted in a significant decline in WM accuracy, and interestingly, a concurrent improvement in incidental LTM. Neural data revealed that, in task blocks, when participants anticipated, and then experienced, increased demands, they engaged medial temporal lobe (MTL) regions more during both the encoding and delay periods. Overall, these results indicate that distinct memory systems are recruited based on anticipated demands of a memory task, and MTL involvement underlies the observed dissociation between WM and LTM performance.

Key words: delayed recognition, fMRI, medial temporal lobe, prefrontal cortex, task difficulty

Introduction

Theories and models of memory have undergone many transformations since the seminal work of [Atkinson and Shiffrin \(1971\)](#), which described a framework in which all memories must pass through short-term memory in order to enter long-term stores. In addition, terminology for the storage of information over different time scales has been reconceptualized many times. Here, we consider the theoretical constructs of working memory (WM), defined as the temporary, short-term storage and/or manipulation of information over a brief delay (seconds) ([Baddeley and Hitch 1974](#); [Baddeley 2000](#)), and long-term memory (LTM) as the consolidation of information for recall at a later time (beyond minutes). Studies involving brain injury have indicated that WM and LTM performance are often dissociable, such that damage to the medial temporal lobe (MTL), specifically the hippocampus, causes anterograde amnesia, a severe LTM deficit ([Milner 1966](#)), while WM may be intact in these individuals ([Drachman](#)

and [Arbit 1966](#); [Milner 1966](#)). The dissociation between WM and LTM has been supported by human neuroimaging research that has shown the MTL to be involved in LTM ([Squire 1992](#)), whereas the prefrontal cortex (PFC) is involved in the maintenance and manipulation processes of WM ([D'Esposito et al. 2000](#); [D'Esposito 2007](#)). However, recent research has suggested that it is difficult to clearly delineate the boundary of memory subtypes, such as when WM ends and LTM begins, and how they interact [reviewed in [Jonides et al. \(2008\)](#)]. Specifically, there is accumulating evidence that the MTL is also engaged in WM tasks ([Ranganath et al. 2003, 2005](#); [Ranganath and Blumenfeld 2005](#); [Axmacher et al. 2007, 2008](#)) and the PFC is active during LTM encoding and retrieval ([Ranganath et al. 2005](#); [Blumenfeld and Ranganath 2007](#); [Wais et al. 2010, 2012](#)). The finding that both the PFC and MTL are engaged in WM and LTM processes suggests that these 2 memory systems are not entirely independent of one another ([Ranganath and Blumenfeld 2005](#)).

If WM and LTM processes overlap, the question arises as to what factors mediate the dominant memory system that is engaged during an interaction with our environment when the goal is to retain information. One approach to assess this is to evaluate whether memory systems are differentially recruited to support performance when one of the systems is overloaded. Previous studies have revealed that there are several experimental manipulations of the delayed-recognition paradigm, frequently used to assess WM, which increase task demands and result in diminished WM performance. For example, WM accuracy declines when memory load is increased (Rissman et al. 2009), when delay periods are lengthened (Curtis and D'Esposito 2003), and when distraction is introduced (Clapp et al. 2010; Clapp and Gazzaley 2012). These task manipulations are interpreted as challenging WM maintenance processes required to actively hold information in mind. Results from 2 studies converge to suggest that such manipulation of task demands results in tradeoffs between PFC and MTL engagement (Rissman et al. 2008; Shrager et al. 2008). However, it has not yet been documented if task demands also drive a tradeoff in WM and LTM performance, and if this occurs in the setting of a concurrent neural dissociation.

The aim of the current behavioral and functional magnetic resonance imaging (fMRI) experiments was to assess the presence, and neural basis, of a dissociation between WM and incidental LTM performance in response to a series of "Challenge" manipulations of a delayed-recognition task. These were presented in separate blocks, so participants could anticipate the task demands prior to each trial, and involved: 1) Manipulating the length of delay between memory encoding and probe, 2) adding distraction during the delay period, and 3) increasing the difficulty of discrimination required at the memory probe by closely matching encoded and probed stimulus features (Fig. 1).

Materials and Methods

Study 1: Behavioral Experiments

Participants

Forty-three young healthy adults (ages 18–29, $M = 22.5$, 29 males) with normal or corrected-to-normal vision volunteered, gave consent, and were monetarily compensated to participate in the study. Two different behavioral experiments utilizing face delayed-recognition tasks were performed (unique participants in each experiment) to determine if manipulations of the demands of the task result in a tradeoff between WM and LTM performance. The first experiment involved a distraction manipulation and the second experiment involved delay period duration manipulation.

Stimuli

The stimuli consisted of grayscale images of faces and were novel across all tasks, across all blocks, and across all trials of the experiment. The stimuli consisted of a variety of neutral-expression male and female faces across a large age range. Hair and ears were removed digitally, and a blur was applied along the contours of the face as to remove any potential nonface-specific cues. All images were 225 pixels wide and 300 pixels tall (14×18 cm) and were presented foveally, subtending 3° of visual angle from fixation.

Tasks

Common across both experiments, participants were shown a face for 800 ms (encode), and after a delay (time period from offset of encode stimulus to onset of probe stimulus) they were shown a second face and then indicated with a button press

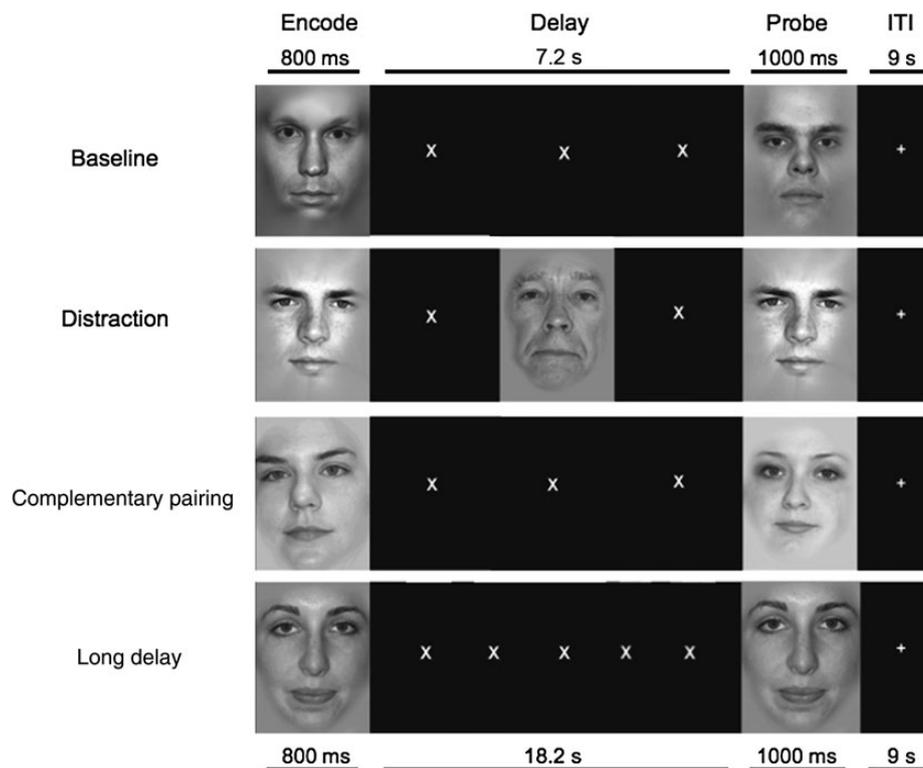


Figure 1. fMRI experimental paradigm. Each experiment consisted of 2 blocks for each of the 5 tasks. The Passive View task (not displayed) was similar to the Baseline task, but displayed an arrow as the probe stimulus. Participants were instructed before each block which task they were going to perform. Note: an additional task (Short Delay, not displayed) was included in the behavioral study.

whether it was a match or nonmatch (Fig. 1). Participants were instructed to respond as quickly as possible without sacrificing accuracy, yielding the measure of WM accuracy. The “Baseline” task in both experiments utilized a delay period of 7.2 s and serves a comparator for the manipulations. Each experiment consisted of 2 blocks of each task with 25 trials per block resulting in 50 trials per task. Blocks were presented pseudorandomly so that each task was run once before any task was run twice, and the 2 middle blocks were never the same. All task blocks were counterbalanced across participants. Participants were instructed before each block which task they were going to perform. About 60% of the trials were nonmatching. This distribution was selected to have a near 50% probability, yet highlighting the differences between the Baseline and Complementary Pairing tasks during the fMRI study (detailed below), which only differed based on nonmatched stimuli.

Experiment 1: Distraction Manipulation. In this experiment (20 participants), there were 2 tasks (4 total blocks). The first was the Baseline task and the other was a distraction task, which included an additional face presented for 1 s in the middle of the 7.2-s delay that was completely irrelevant to the delayed-recognition task. Participants were instructed to ignore the distracting face to the best of their ability without diverting their gaze or closing their eyes. They were instructed to foveate on the continuously present fixation cross in the center of the screen.

Experiment 2: Delay Duration Manipulation. In this experiment (23 participants), there were 3 tasks (6 total blocks), which varied the length of the delay period both shorter and longer than the duration of the delay in the Baseline task: delay periods were 3.2 s (short delay), 7.2 s (Baseline), or 18.2 s (long delay).

Incidental Long-Term Memory

Fifteen minutes after the completion of the delayed-recognition task, a surprise incidental LTM test was administered where participants viewed 30 encode face stimuli from each task along with the same number of novel face stimuli that were not presented during the primary experiment. No encode stimuli were included that were also a match during the main experiment (i.e., no stimulus in the post-experiment test was viewed more than once in the main experiment). All stimuli (both novel stimuli and stimuli from the experiment) were randomly ordered, and the participants were asked to give a confidence judgment reflecting the degree to which they believed each image was old or new (1 = definitely new, 2 = probably new, 3 = probably old, and 4 = definitely old). This section of the experiment was self-paced. The summary statistic used for this task took each participant's average rating for each task and subtracted their average rating for novel stimuli from each of the task averages, thus creating an LTM index that was independent of response biases.

Study 2: fMRI Experiment

Participants

Twenty-two young healthy adults (ages 18–31, $M = 23.85$, 11 males) with normal or corrected-to-normal vision volunteered, gave consent, and were monetarily compensated to participate in the study. Participants were prescreened to ensure that the sample did not include anyone with psychological or neurological disorders, brain injuries, or under the influence of medication known to affect cognitive state. Two participants were removed from the analyses due to significant drop-out of blood oxygen level-dependent (BOLD) signal.

Stimuli

Same as described in Study 1.

Tasks

Similar to Study 1, this experiment uses a delayed-recognition task involving grayscale face images, and includes the same general task manipulations of distraction and delay period duration manipulation. However, the short delay was not included because it would not allow adequate time for the BOLD response to summate. The final manipulation involved stimulus discriminability during recognition based on the similarity between encode and probe stimuli. The specifics of the tasks were as follows (Fig. 1).

Baseline. The delayed-recognition task that serves as the baseline had a delay period of 7.2 s and minimal steps were taken in matching the encoded and probe stimuli. We will refer to this as basic pairing, and involves matching race, gender, and age.

Long Delay. Basic pairings were used along with a long delay (18.2 s) in this task.

Distraction. Basic pairings were used along with the Baseline delay duration (7.2 s), but the addition of an irrelevant, novel face appearing for 1 s in the middle of the delay.

Complementary Pairing. Closely paired encoded and probe images were used along with the Baseline delay (7.2 s) in this task. Complementary Pairings between the features of the encoded and probe stimuli were generated manually based on multiple parameters of the images including race, gender, age, head orientation, luminance, image resolution, and salient facial features. To ensure the Complementary Paired stimuli were more similar than the stimuli used in the Baseline task, an independent group of 5 healthy young adults (aged 23–37 years, $M = 29.8$, 3 males) assessed 40 paired stimuli that were randomly selected from the Baseline and Complementary Pairing tasks (20 from each task). On each trial, the 2 stimuli were presented sequentially for 1 s each with a 1-s interstimulus interval. Participants were instructed to respond to the second stimulus as to how similar it was to the first stimulus based on a 4-point Likert scale (1 = very dissimilar, 2 = somewhat dissimilar, 3 = somewhat similar, and 4 = very similar). All 5 participants verified that the Complementary Paired stimuli were assessed to be more similar ($M = 2.94$, $SEM = 0.21$) than the Baseline task stimuli ($M = 1.87$, $SEM = 0.16$; $t_{(4)} = 12.44$, $P < 0.0005$).

Passive View. This task was included to serve as a metric for each participant's visual evoked response to viewing the stimuli. The stimulus and timing were similar to the Baseline task; however, the probe stimulus was a left or right pointing arrow indicating which button the participant should press. Participants were instructed to passively view the face stimuli without trying to remember them and respond to the probe arrow as quickly and accurately as possible.

The collective term for all tasks, except Baseline and Passive Views, will be referred to as “Challenge” tasks. Each experimental session comprised 2 blocks of the 5 tasks (15 trials/block; 10 total blocks; 30 total trials per task), pseudorandomly presented so that each task was run once before any task was run twice, and the 2 middle blocks were never the same. All task blocks were counterbalanced across participants. Participants were instructed before each block which task they were going to perform.

Incidental LTM. Fifteen minutes after completing the experimental tasks, a surprise LTM test was administered outside of the scanner as described in Study 1 with 144 faces, including 18 encode stimuli from each task except passive view (72 encode stimuli) and 72 novel stimuli.

fMRI Acquisition and Processing

All images were acquired on a Siemens 3-T Trio Magnetom. Images were collected with a 2-s time repetition (TR) and $1.78 \times 1.78 \times 3.5$ mm voxel size. For our functional data, we collected 33 3.0 mm oblique axial T_2^* -weighted gradient-echo slices (TR = 2000 ms, 25 ms time echo, 90° flip angle, and 250 mm^2 field of view in a 128×128 matrix). Images were corrected for slice acquisition timing, motion artifacts, and spatially filtered using a 5-mm full-width at half-maximum Gaussian smoothing kernel. Data were analyzed using SPM5 in participant-native space. Group whole-brain maps were calculated from MNI-normalized data. In addition, high-resolution structural (T_1 -magnetization-prepared rapid gradient-echo) images were collected.

Data Analysis

fMRI Univariate Analysis. BOLD responses were modeled as epochs of neural activity by using 3 separate regressors for the encode, delay, and probe periods, which were convolved with the canonical hemodynamic response function (HRF). All epochs were modeled with the SPM5 canonical HRF convolved with a boxcar function with a duration of one TR. The onsets of temporally adjacent covariates were spaced at least 3.6 s apart to minimize the contamination of residual activity and auto-correlation (Zarahn et al. 1997). Thus, delay regressor onsets were placed at the midpoint of the delay period, whereas the encode and probe regressors were placed at the onset of the respective stimuli. Additionally, 6 motion regressors were included to control for possible participant movement (X, Y, Z, roll, pitch, yaw). All trials (correct and incorrect) were modeled with the same regressor, though trials where participants failed to respond to the probe were modeled with a separate regressor and excluded from the final analysis. Comparisons between combined Challenge tasks and Baseline were appropriately weighted to render a valid contrast (i.e., Long Delay + Distractor + Complementary Pairing tasks – $3 \times$ Baseline task).

Region-of-Interest Localization. A separate functional localizer task was conducted prior to the main fMRI tasks, which was used to identify the fusiform face area (FFA), a face-selective area in the visual association cortex (Kanwisher et al. 1997). In this task, participants performed a 1-back task during 16-s blocks of face stimuli (5 blocks) and scene stimuli (5 blocks). Blocks of face and scene stimuli were separated by 16 s of rest and presented in an alternating order. Participants were instructed to indicate when a match (1-back) occurred within a block with a simple key press. Face and scene stimuli regressors consisted of a boxcar function extending across the 16-s block of stimuli and were convolved with the SPM5 canonical HRF. Face and scene stimuli regressors were then contrasted to generate SPM[T] images, and from these contrasts, region of interests (ROIs) were defined. A face-selective ROI (FFA) was then identified as the cluster of 35 contiguous voxels with the highest t-value within the right fusiform gyrus of each participant. The decision of the ROI voxel extent was based on the methodology of similar studies (Leppanen et al. 2004; Fischer et al. 2005; Clapp et al. 2010; Rota et al. 2009; Clapp and Gazzaley 2012) and was chosen in order to achieve a reasonable balance between regional specificity (diminished by the use of a larger cluster) and susceptibility to noise (a problem with smaller ROIs). The

right FFA has been shown to be most strongly activated by faces (Bentin et al. 1996; Kanwisher et al. 1997).

fMRI Functional Connectivity Analysis. A new general linear model (GLM) design matrix was constructed in which each stage (encode, delay, and probe) of each trial was coded with a unique covariate, consistent with previous work (Clapp et al. 2010, 2011; Bollinger et al. 2010; Wais et al. 2010; Zanto et al. 2010; Chadick and Gazzaley 2011; Zanto et al. 2011). The placement and duration of the regressors were the same as that used in the univariate analysis. However, whole-brain maps of functional connectivity were generated by extracting mean β -values for each stage of every trial from each participant's FFA ROI (averaged over the ROI voxels) and correlating these β -values across all trials (correct and incorrect, except no response trials) with every voxel in a whole-brain analysis (Gazzaley et al. 2004; Rissman et al. 2004). This was done separately for each condition.

Previous work has suggested that, due to excessive supra-threshold voxels caused by local auto-correlations (Clapp et al. 2010) among other factors (such as vasculature or machine noise), there exists a possibility that the resultant correlation maps may not be amenable to parametric testing. To circumvent this issue, a nonparametric permutation test was employed to generate whole-brain contrast maps between each Challenge task and the Baseline task, separately. This involved conducting an iterative sign-inversion procedure that calculated significance over the course of 10 000 iterations (Nichols and Holmes 2002; Bollinger et al. 2010; Bollinger et al. 2011).

Our primary interest was to identify patterns that were consistent across like contrasts. To that end, Challenge > Baseline contrasts and Baseline > Challenge contrast maps were created by separately conjoining the component contrasts for each task stage (e.g., Challenge > Baseline = Long Delay > Baseline and Distractor > Baseline and Complementary Pairings > Baseline), in accordance with previously established conjunction methodology using Fisher's method (Fisher 1950; Lazar et al. 2002; Dolcos et al. 2008; Giovanello et al. 2010; St Jacques et al. 2010). Briefly, Fisher's method combines multiple test statistics (P -values) into one-test statistic using the formula: $T_F = -2 \sum \log(P)$, where P is a set of P -values with k elements, \log denotes the natural logarithm, and T_F reflects Fisher's conjoined test statistic that is compared with a χ^2 distribution with $2k$ degrees of freedom. Each of the 6 (2 conjunctions \times 3 task stages) statistical maps used for the conjunction analysis were subjected to a cluster extent-based correction for multiple comparisons. To match the thresholding procedure of the univariate analysis, the pooled significance threshold of the conjoined statistical maps was equal to or surpassed an elemental alpha of $P < 0.005$, computed using a modified version of Fisher's method of estimating conjoint significance. The modification entailed a requirement for each voxel of the component images to reach individual significance, thus ensuring that outliers would not skew the resulting conjunctions.

Correction for Multiple Comparisons. Where applicable, behavioral and neural data were corrected for multiple comparisons. Corrections for behavioral data utilized a false discovery rate method (Benjamini and Hochberg 1995), whereas neural data were corrected through a Monte Carlo simulation that was employed using AlphaSim from the AFNI toolbox (Cox 1996). Clusters were defined using the default linkage radius (nearest-neighbor, 6-connected voxel neighborhood) and a voxel-wise alpha of $P \leq 0.005$. Corrections were mask-delimited based on a priori hypotheses regarding regional involvement derived from previous

research (i.e., small volume correction) (Worsley et al. 1996; Brett et al. 2003; Lamm et al. 2004; Viard et al. 2007). Masks were created using the software package WFU_pickatlas (Lancaster et al. 2000; Maldjian et al. 2003). Specifically, masks of the MTL, PFC, and all noncerebellar gray matter (GM) were utilized. The MTL mask included bilateral hippocampus and parahippocampus (Supplementary Fig. 1A), whereas the PFC mask included all GM within and anterior to the precentral gyrus (Supplementary Fig. 1B). The correction employing the GM mask will be referred to as a whole-brain correction since, for the purposes of fMRI data interpretation, our hypotheses and interest lay solely within this tissue class.

Results

Study 1: Behavioral Experiments

In Experiment 1, WM accuracy dropped significantly when participants were faced with distracting stimuli presented in the middle of the delay period relative to performance on a Baseline task (Baseline—96%, Distractor—93%; $t_{(19)} = 2.77, P < 0.05$). In contrast, the incidental LTM test revealed that participants remembered the encoded stimuli better in the Distractor task (Baseline—0.013, Distractor—0.25; $t_{(19)} = 2.39, P < 0.05$; Fig. 2A).

In Experiment 2, WM accuracy was influenced by the length of the delay period, such that participants did best on the short delay (91%), followed by the medium delay (Baseline, 88%), and then the long delay (83%) exhibited the least accurate WM performance (see Fig. 2B for individual comparisons: Short Delay > Medium Delay and Long Delay, Medium Delay > Long Delay; all 3 comparisons $t_{(22)} > 2.43, P < 0.05$). Similarly, response times were fastest following the short delay ($M = 819$ ms, $SEM = 53$ ms), slower following the medium delay ($M = 881$ ms, $SEM = 50$ ms), and slowest after the long delay ($M = 970$ ms, $SEM = 55$ ms; all 3 comparisons $t_{(22)} > 4.76, P < 0.01$). Thus, accuracy and response time data both show WM performance declines with an increasing delay period. However, incidental LTM performance showed the opposite pattern, such that encode stimuli were remembered best in the long delay task (0.51), followed by the medium delay

task (0.41) and then the short delay task (0.29) exhibited the least accurate LTM performance (see Fig. 2B for individual comparisons: Long Delay > Medium Delay and Short Delay, Medium Delay > Short Delay; all 3 comparisons $t_{(22)} > 2.41, P < 0.05$).

Taken together, these 2 experiments demonstrate a tradeoff between WM and LTM performance as a function of delayed-recognition task demands. With increasing demands, whether due to longer delay periods or the presence of a distraction, there was a decline in WM accuracy concomitant with an increase in LTM performance. Thus, these results provide novel evidence of a dissociation between WM and LTM performance based on task demands, and establish the utility of these task manipulations to examine the neural basis of this dissociation in Study 2.

Study 2: fMRI Experiment

Behavioral Performance

The WM performance results in the fMRI experiment revealed that, as predicted and consistent with Study 1, participants performed best on the Baseline task, such that accuracy for all Challenge tasks (Long-Delay, Distraction, and Complementary Pairing—a new challenge in Study 2) was significantly reduced relative to Baseline levels (i.e., WM accuracy during Baseline task > Long-Delay, Distraction, and Complementary Pairing; all 3 comparisons $t_{(21)} > 2.26, P < 0.05$; Fig. 2C). Of note, there were no significant differences between any of the Challenge tasks (i.e., Long-Delay = Distraction = Complementary Pairing; all 3 comparisons $t_{(21)} < 1, P > 0.05$). Similar to accuracy data, response times during the Baseline task ($M = 1021$ ms, $SEM = 54$ ms) were faster than those for all 3 Challenge tasks (all 3 comparisons $t_{(21)} > 2.45, P < 0.05$). Moreover, no differences were observed in response times between the Complementary Pairing ($M = 1066$ ms, $SEM = 48$ ms) and Distraction ($M = 1073$ ms, $SEM = 45$ ms) tasks ($t_{(21)} < 1, P > 0.05$), whereas the Long-Delay task ($M = 1148$ ms, $SEM = 57$ ms) resulted in slowed response times compared with all other tasks (all 3 comparisons $t_{(21)} > 2.45, P < 0.05$). Although it is unclear why the Long Delay resulted in slowed responses compared with the other Challenge tasks, the response time and accuracy data both show that, compared with the

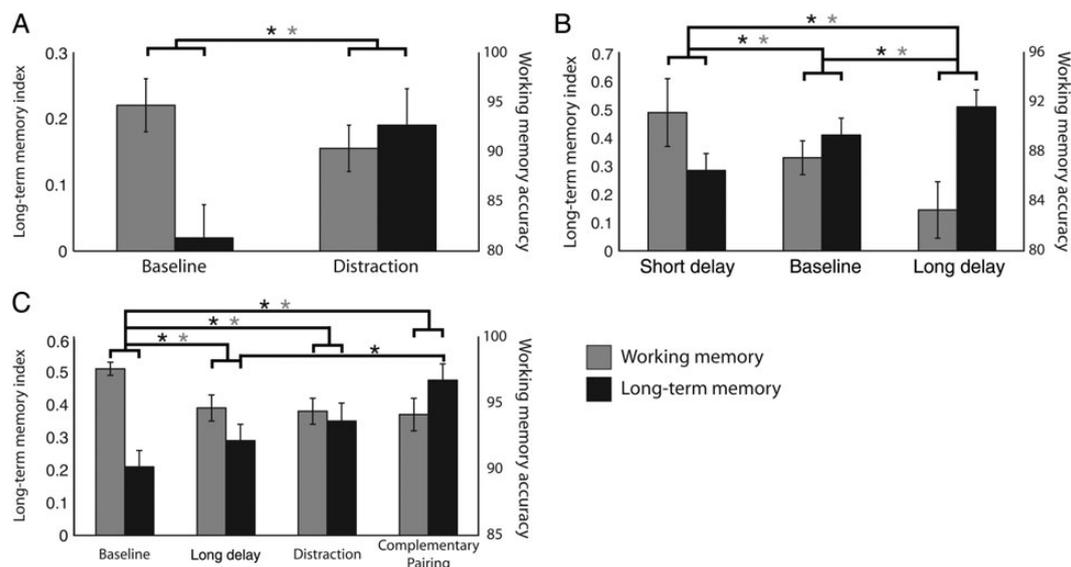


Figure 2. Behavioral results. Study 1—Behavioral experiments: (A) Baseline versus Distraction, (B) Baseline versus Short and Long Delays. Study 2—fMRI experiment: (C) Baseline versus Distraction, Long Delay and Tight Pairing. Gray asterisks represent LTM comparisons with $P < 0.05$; black asterisks represent WM accuracy comparisons with $P < 0.05$.

Baseline task, WM performance declines when participants are challenged.

In contrast, incidental LTM of the encode faces presented in all the Challenge tasks was significantly better than that of the Baseline task (i.e., LTM accuracy during Baseline task < Long Delay, Distraction, and Complementary Pairing; all 3 comparisons $t_{(21)} > 2.14$, $P < 0.05$). The only difference in LTM between Challenge tasks was that encoded stimuli from the Complementary Pairing task were recognized better than those from the Long-Delay task ($t_{(21)} = 2.89$, $P < 0.05$). Although it is unclear why these 2 Challenge tasks exhibited a LTM difference and not a WM accuracy difference (unlike the behavioral studies), this may be a product of the distracting fMRI environment altering WM performance or possibly due to the differential sample sizes between the behavioral studies (50 trials) and the fMRI study (30 trials). It could be argued that different LTM performance between these Challenge tasks reflects different levels of task difficulty. However, the only goal of participants in performing these tasks was to remember information over the short term, and thus the assessment of WM accuracy, which did not differ between these Challenge tasks, suggests that they were balanced in terms of difficulty. Nonetheless, the behavioral results from the fMRI experiment were overall consistent with the memory performance results of the 2 behavioral experiments, confirming a dissociation between WM and LTM performance with shifting task demands.

Univariate fMRI

To investigate the neural underpinnings of the memory performance dissociation described above, we examined BOLD univariate measures from the encode and delay stage of the delayed-recognition tasks separately. Since the Challenge tasks were all different from Baseline and largely comparable in difficulty as indicated by performance measures, analysis of the neural data combined the 3 task manipulations and collectively compared them with the Baseline task (see Materials and Methods for details of our approach). We focused our analysis on the PFC and the MTL since these areas are well known to play an important role in WM and LTM processes (Ranganath et al. 2003; Ranganath and Blumenfeld 2005; Blumenfeld and Ranganath 2006; Axmacher et al. 2007, 2008; Berryhill and Olson 2008a, 2008b). Regions

within these search areas with significantly different activity patterns for planned contrasts will be described below [multiple comparisons addressed using small volume corrections (Cox 1996); univariate encoding and delay data shown in Table 1]. For a complete list of brain regions that revealed differential activation between the Challenge and Baseline tasks from a whole-brain analysis, see Supplementary Tables.

Encode Period Activity. During the encode period, we observed widespread differential activation throughout the brain between the Baseline and Challenge tasks (Supplementary Table 1). Importantly, greater MTL activation (specifically, in the left hippocampus; $-23 -9 -21$ MNI and right parahippocampus; $19 -25 10$ MNI) was observed for the Challenge tasks in comparison with the Baseline task (Fig. 3A, $P < 0.05$). In addition, a region within the PFC, the right middle frontal gyrus (MFG; $30 16 55$ MNI), also exhibited greater activity in the Challenge tasks compared with the Baseline task ($P < 0.05$). In the reverse comparison, the inferior frontal gyrus showed more activation in the Baseline task compared with the Challenge tasks ($P < 0.05$), whereas no areas of the MTL exhibited this pattern. Of note, the MTL was significantly more active during the Baseline task compared with either a passive view task or the intrinsic GLM baseline ($P < 0.05$).

Delay Period Activity. Similar to encode period activity, we observed widespread differential activation throughout the brain between the Baseline and Challenge tasks during the delay period (Supplementary Table 2). Notably, there were several areas in both the MTL and PFC that exhibited more activation in the Challenge tasks compared with the Baseline (Table 1). In assessing areas that were more active in the Baseline task, PFC regions in the MFG, precentral, and anterior cingulate gyrus ($P < 0.05$) were more active compared with the Challenge tasks, with no MTL regions exhibiting greater Baseline activity (Fig. 3B). Of note, activity in the parietal cortex exhibited a similar relationship as the PFC, such that the Challenge and Baseline tasks displayed differential activity profiles that did not clearly dissociate with regard to task demands (Supplementary Table 2).

In summary, during the encoding and maintenance processing stages of the delayed-recognition tasks, several PFC regions were more active during the Baseline task, whereas others were

Table 1 Univariate activity

Stage	Contrast	Lobe	Region label	BA	Volume (mm ³)	X	Y	Z
Encode	Challenge > Baseline	Frontal	Middle frontal gyrus	8	216	30	16	55
			Temporal	Hippocampus	35	256	-23	-9
		Parahippocampal gyrus	30	200	18	-8	-28	
			Parahippocampal gyrus	30	104	20	-26	-14
	Baseline > Challenge	Frontal	Supplementary motor	23	224	-4	-9	50
			Frontal orbital gyrus	47	176	27	26	-16
			Insula	48	144	38	-8	-4
			Inferior frontal gyrus	47	128	-46	35	2
			Superior frontal gyrus	8	192	20	24	58
			Inferior frontal orbital	47	144	45	35	-9
Delay	Challenge > Baseline	Frontal	Middle frontal orbital	11	120	-31	53	-2
			Precentral gyrus	4	120	57	1	43
			Anterior cingulate gyrus	24	336	1	10	40
			Precentral gyrus	4	216	-41	-15	62
	Baseline > Challenge	Frontal	Precentral gyrus	6	128	-25	-10	60
			Anterior cingulate gyrus	24	120	0	3	46
			Middle frontal gyrus	46	120	-33	34	39

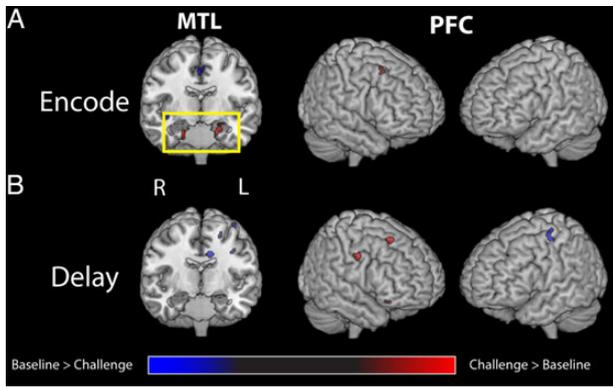


Figure 3. Univariate BOLD activity. (A) During the encode period, MTL activity was increased in the Challenge tasks compared with the Baseline task (yellow box). (B) During the delay period, Challenge and Baseline tasks utilize differential PFC regions (Table 1).

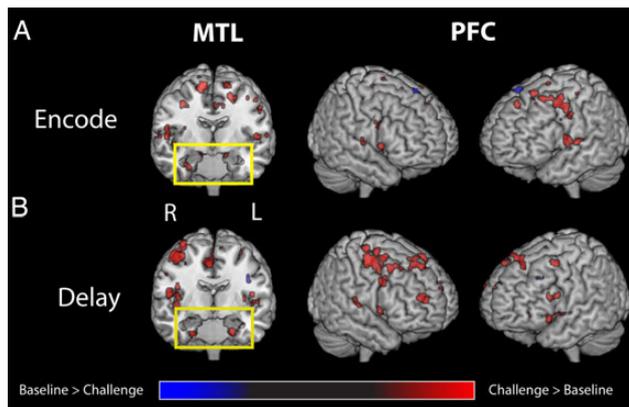


Figure 4. Functional connectivity data. Functional connectivity between the FFA and MTL increased in the Challenge tasks compared with the Baseline task during (A) the encoding period as well as during (B) the delay period (yellow boxes). Challenge tasks and Baseline task exhibit differential functional connectivity between FFA and PFC, although much more widespread during Challenge tasks (Table 2).

more active during the Challenge tasks, but the MTL was more active only during Challenge tasks versus Baseline (i.e., hippocampus in encoding, and parahippocampal gyrus in encoding and delay).

fMRI Functional Connectivity

To assess network differences associated with face processing across tasks, we used the beta-series functional connectivity approach (Gazzaley et al. 2004; Rissman et al. 2004) to compute MTL and PFC functional connectivity with a face-selective visual cortical seed region (i.e., FFA; Kanwisher et al. 1997). During the encode period, we observed widespread functional connectivity between the FFA and the rest of the brain, which differed between the Baseline and Challenge tasks (Supplementary Table 3). Importantly, FFA functional connectivity with multiple subregions of the MTL (i.e., parahippocampal gyrus) was greater for Challenge tasks compared with Baseline ($P < 0.05$, corrected; Fig. 4A), whereas there were no MTL regions that exhibited greater functional connectivity with the FFA in the Baseline task (Table 2). Additionally, FFA functional connectivity with the PFC was more widespread during Challenge tasks (10 PFC regions

exhibited Challenge > Baseline, see Table 2) compared with the Baseline task (3 PFC regions exhibited Baseline > Challenge, see Table 2). Interrogation of the delay period revealed a similar pattern, such that functional connectivity between the FFA and the rest of the brain was widespread and differed between the Baseline and Challenge tasks (Supplementary Table 4). Notably, functional connectivity between the FFA and MTL regions was greater in the Challenge tasks, whereas there were no MTL regions that exhibited greater functional connectivity with the FFA in the Baseline task (Fig. 4B). Additionally, FFA functional connectivity with the PFC was more widespread during Challenge tasks (12 PFC regions exhibited Challenge > Baseline, see Table 2) compared with the Baseline task (2 PFC regions exhibited Baseline > Challenge, see Table 2). Of note, functional connectivity between the FFA and parietal cortex exhibited a similar relationship as the PFC, such that the Challenge and Baseline tasks displayed differential connectivity profiles (Supplementary Tables 3 and 4).

To explore a neural-behavioral relationship, MTL regions that exhibited significant univariate activity or functional connectivity to the FFA were correlated with LTM scores across participants. However, neither the univariate data nor the functional connectivity data from the MTL exhibited a significant correlation with LTM performance. Therefore, it is likely that other factors in addition to MTL recruitment also contribute to the change in LTM performance based on the expected task demands.

Overall, the functional connectivity data revealed the same pattern as the univariate data, and support the conclusion that the dissociation between WM and LTM was associated with greater recruitment of MTL networks in the encoding and delay periods of delayed-recognition tasks in the setting of increased task demands.

Discussion

This study provides neural and behavioral evidence of a dissociation between the engagement of WM and LTM systems based on the demands of a brief duration memory task. Specifically, we demonstrate and replicate using several manipulations of a face delayed-recognition task that increased demands (i.e., longer delay period, distraction during delay period, and similarity of encode and probe stimuli) all result in lower WM accuracy, but higher LTM recognition of the same stimuli (a push-pull pattern was documented in the behavioral experiments). These results indicate that distinct memory systems are differentially involved when individuals engage in delayed-recognition tasks of varying difficulty. It is important to note that task manipulations were presented in blocks, allowing participants to anticipate the challenge of each task prior to their engagement (rather than unexpectedly being presented with a distractor, long delay, or a difficult pairing). The data suggest that expectations of task demands in an experimental block underlie our findings. This is most clearly highlighted by noting that the encode stage was perceptually identical for all tasks and so the only factor that differed during encoding between tasks was the participant's expectation of what they would encounter later in the trial. Therefore, it could only be expectation of task demands that drove the increased MTL recruitment during the encode stage of the Challenge tasks.

Our interpretation of these findings is that the anticipation of increased difficulty in accomplishing WM task goals leads to a shift in the engaged neural circuitry in an attempt to preserve high-level performance. This shift, however, is clearly not entirely effective in maintaining WM performance, as documented by diminished WM accuracy in the challenge conditions, but it does result in the unintended consequence of stronger LTM encoding

Table 2 Functional connectivity

Stage	Contrast	Lobe	Region label	BA	Volume (mm ³)	X	Y	Z
Encode	Challenge > Baseline	Frontal	Anterior cingulate gyrus	24/32	1568	-7	11	40
			Supplementary motor area	6	968	8	11	55
			Superior frontal gyrus	6	488	11	-4	67
			Precentral gyrus	4	432	3	-27	61
			Precentral gyrus	4/6	400	19	-18	67
			Superior frontal gyrus	6	288	-18	1	68
			Middle frontal gyrus	6/9	272	-37	18	58
	Baseline > Challenge	Frontal	Precentral gyrus	9/44	272	48	9	29
			Precentral gyrus	6	240	-53	4	38
			Precentral gyrus	9/48	216	-63	5	12
			Parahippocampal gyrus	36	1008	27	1	-28
			Parahippocampal gyrus	30	968	-28	-20	-22
			Parahippocampal gyrus	20	688	26	-18	-23
			Subcallosal gyrus	11	296	7	28	-12
Delay	Challenge > Baseline	Frontal	Superior frontal gyrus	8	240	2	33	65
			Insula	13/48	216	38	4	10
			Precentral gyrus	6	6968	34	-2	52
			Medial frontal gyrus	6	1288	-4	-15	58
			Precentral gyrus	3/4	712	44	-14	49
			Superior frontal gyrus	6	672	-1	15	58
			Inferior frontal orbital	47	480	-48	22	-1
	Baseline > Challenge	Frontal	Anterior cingulate	24	384	-3	3	41
			Central opercular	48	368	-49	-2	5
			Superior frontal gyrus	10/46	320	33	60	21
			Anterior cingulate	24	312	-9	14	36
			Middle frontal gyrus	6	280	32	7	64
			Superior frontal gyrus	6	232	-10	1	69
			Paracingulate gyrus	24/32	208	-9	13	50
Challenge > Baseline	Temporal	Hippocampus	35	1064	-26	-20	-22	
		Parahippocampal gyrus	30	640	24	-4	-36	
		Parahippocampal gyrus	30	600	-24	-2	-28	
		Parahippocampal gyrus	30	408	22	-22	-28	
		Precentral gyrus	48	448	-45	-8	29	
		Middle frontal gyrus	46	208	-39	27	43	

(note: unintended in that there were no LTM goals). The fMRI results support this interpretation and inform the mechanistic basis of the behavioral dissociation by revealing that MTL regions exhibit increased activity and functional connectivity with visual cortical areas during both the encoding and delay periods of the more challenging tasks relative to the Baseline task. This finding is consistent with the well-documented role of the MTL in LTM consolidation processes (Alvarez and Squire 1994). Moreover, these findings support research indicating that hippocampus-dependent WM is beneficial for LTM encoding (Axmacher et al. 2009) and that hippocampal activity prior to stimulus presentation predicts subsequent LTM performance (Park and Rugg 2010). Thus, this study reveals that expectations of difficulty in performing a brief duration memory task influence the neural networks engaged, resulting in a dissociation between WM and LTM performance.

We observe that the MTL is more active and exhibits greater functional connectivity with stimulus-selective visual cortical areas in the Challenge tasks during encoding and delay periods, with no examples of the reverse pattern (see Figs 3 and 4, yellow boxes). This dissociation suggests MTL engagement as a putative underlying neural correlate of the observed behavioral dissociation. In contrast, PFC activity and functional connectivity does not clearly dissociate across tasks, that is, different regions of the PFC are more engaged by both Challenge and Baseline tasks. And so, we do not have a clear neural indicator of disrupted

PFC-mediated WM maintenance processes in the Challenge tasks, as we hypothesized. We suspect this is due to different PFC subregions being engaged by the many control processes mandated by these tasks, thus masking simple interpretations of distinct contributions of PFC regions to WM processes. This complexity may help explain why the FFA exhibited more widespread functional connectivity to the PFC during the Challenge tasks. Additionally, consistent with the parietal lobe previously being shown to be involved in both WM and LTM (Berryhill and Olson 2008a, 2008b; Uncapher and Wagner 2009; Cabeza et al. 2011, 2012; Uncapher et al. 2011;), the pattern of activation in these regions also did not consistently dissociate with regard to task demands.

The data suggest that the MTL was more engaged when simple maintenance was not anticipated to be sufficient for task performance, as in the Challenge scenarios when delay durations were long, when distraction interrupted the WM maintenance period, and when there was a need for high levels of details of a stored representation. This raises the question as to why the hippocampus was engaged in the setting of increased WM demands. One possibility is suggested by previous findings that show the hippocampus to be critical in forming relationships between items and representation binding (Cohen and Eichenbaum 1993; Cohen et al. 1997; Davachi and Wagner 2002; Preston et al. 2004). Perhaps, when the opportunity for rote maintenance (e.g., visualization) is diminished, the act of encoding associations between face

features (e.g., the spatial relations between eyes and nose of a face) makes subsequent recognition of the face probe more effective (Morris et al. 1977). If participants were driven to store relational data in an attempt to optimize their memory in the setting of these challenges (even if subconsciously), then MTL engagement used to accomplish this act might lead to stronger subsequent LTM as an unintended consequence, as there were no LTM goals. This is not to say that the LTM system was accidentally engaged or that it does not operate independent of the WM system. Rather, knowledge of increased task difficulty resulted in a shift in the engaged neural circuitry in an attempt to preserve high-level performance. Although the current data cannot speak to whether this was a conscious effort to “try harder” during the Challenge tasks, it is certainly plausible. Additionally, it should be noted that these data do not support the idea of an antagonistic relationship between WM and LTM, as decreased WM performance was not correlated with increased LTM performance across participants.

The neural results of the current study are in contrast with findings that MTL was equally active during episodic retrieval and WM tasks (Cabeza et al. 2002), suggesting a similar role for WM and LTM processes. Yet, our data corroborate other research showing increased MTL activity when the WM maintenance period is elongated, resulting in lower WM accuracy (Talmi et al. 2005). The discrepancy between these studies may lie with task difficulty, in that Cabeza et al. (2002) observed >90% accuracy on both WM and episodic retrieval, whereas Talmi et al. (2005) observed <75% accuracy for long WM delays and >90% accuracy for short WM delays. Notably, our current results do show elevated MTL activity during the Baseline task compared with rest; however, MTL activity was increased during Challenge tasks compared with the Baseline task concomitant with decreased WM and increased LTM performance. Thus, task demands, or anticipation thereof, appear to alter the balance of how WM and LTM systems are utilized and may help reconcile disparate results regarding the role of MTL in WM and LTM processes.

The current results are also consistent with evidence from patient populations that show that the MTL is necessary in situations when simple memory maintenance is not possible. Shrager et al. (2008) investigated WM performance in both controls and amnesics and found that both groups were able to maintain face stimuli over delays of 2 and 7 s. However, when the duration of the delay increased to 14 s, the amnesics exhibited a much larger drop in WM performance. These results were interpreted as revealing that amnesics were able to rely on non-MTL-dependent active maintenance processes at short delays, and that there was a reliance on the MTL system in the longer delay tasks. This is entirely consistent with our findings that increased duration of the delay drives reliance on the MTL. Other research with amnesics also supports our results that longer delay durations elicit greater reliance on the MTL (Ranganath and Blumenfeld 2005).

Of interest, another study using a face delayed-recognition task revealed that amnesics were impaired in memory performance when delays were only 7 s (Nichols et al. 2006). Moreover, it was noted by the authors that the stimuli “could not be solved using easily verbalizable features.” This description is reminiscent of the rigorous manner in which we manually paired stimuli in the Complementary Pairings task, which exhibited increased engagement of the MTL over baseline. Additionally, Nichols et al. (2006) reported that no WM differences existed between amnesics and controls with a 1-s delay interval. They also postulated that LTM processes are more relevant at the longer delay. This statement is consistent with our hypothesis that increasing difficulty by manipulating delay duration results in a situation in

which rote maintenance is not sufficient and thus the MTL is recruited. Similarly, another study found that increasing demands in a face delayed-recognition task by increasing the memory load resulted in decreased WM performance and an increase in functional connectivity between the MTL and the visual association cortex (i.e., FFA) during the delay period (Rissman et al. 2008); yet another manipulation that increased delayed-recognition task demands and resulted in MTL network engagement.

It is possible that increased attentional demands increased vasodilation, thereby influencing measures of functional connectivity. This could reflect an increase in arousal and help explain why more neural regions exhibited functional connectivity to the FFA during the Challenge tasks. However, it is unlikely that this reflects a general (non-specific) increase in arousal, as many regions exhibited greater functional connectivity during the Baseline task and even more regions did not dissociate between the task demands. Thus, mean FFA BOLD activity changes (and corresponding vascular state) did not influence functional connectivity measures throughout the brain in a homogeneous manner, as would be expected from a general increase in arousal with a global increase in vasodilation.

It could be argued that, due to the close proximity of the GLM regressors for the encoding and delay periods, auto-correlation could bias the results to be similar across the 2 task stages. Thus, we chose not to directly contrast the encoding and delay periods, nor do we draw strong conclusions about specific neural regions and their role in distinct task stages. Nonetheless, we report data from both the encoding and delay periods because the results showed minimal overlap between task stages in terms of the regions identified as being significantly modulated by task demands. Specifically, univariate BOLD activity exhibited <1% overlap between regions listed in Supplementary Table 1 (encoding activity) and Supplementary Table 2 (delay activity). Similarly, functional connectivity data exhibited only 5% overlap between regions listed in Supplementary Table 3 (encoding) and Supplementary Table 4 (delay). Thus, any confounds introduced by auto-correlations were negligible and we consider results from the 2 task stages as supporting our overall conclusions.

In the current study, manipulations of task demands drive how different memory systems are engaged, and this in turn differentially influences WM and LTM performance. Our results indicate that when participants anticipate a challenging task in which simple WM maintenance is not possible or sufficient, the MTL is more engaged during encoding and maintenance periods. This neural pattern serves to explain the behavioral findings of enhanced LTM in the setting of a task that exhibits diminished WM accuracy. These findings offer another level to Baddeley’s revised theory of memory that introduced an episodic buffer, referred to as transitive memory, which aids in the crystallization of items from WM into LTM (Baddeley 2000). Our results suggest that engagement of the episodic buffer is weighted by task demands, such that increased difficulty in active WM maintenance results in the episodic buffer shunting information to an LTM system.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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Notes

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