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Prefrontal activity associated with working memory and episodic long-term memory

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Abstract

Many recent neuroimaging studies have highlighted the role of prefrontal regions in the sustained maintenance and manipulation of information over short delays, or working memory (WM). In addition, neuroimaging findings have highlighted the role of prefrontal regions in the formation and retrieval of memories for events, or episodic long-term memory (LTM), but it remains unclear whether these regions are distinct from those that support WM. We used event-related functional magnetic resonance imaging (fMRI) to identify patterns of prefrontal activity associated with encoding and recognition during WM and LTM tasks performed by the same subjects. Results showed that the same bilateral ventrolateral prefrontal regions (at or near Brodmann's Areas [BA] 6, 44, 45, and 47) and dorsolateral prefrontal regions (BA 9/46) were engaged during encoding and recognition within the context of WM and LTM tasks. In addition, a region situated in the left anterior middle frontal gyrus (BA 10/46) was engaged during the recognition phases of the WM and LTM tasks. These results support the view that the same prefrontal regions implement reflective processes that support both WM and LTM.

Keywords: Prefrontal cortex; Frontal lobes; Episodic memory; Working memory; Long-term memory; Short-term memory; Executive control; Event-related fMRI; Neuroimaging

1. Introduction

Recent neuroimaging findings have prompted intense interest in the role of prefrontal cortex (PFC) in human memory processes. For example, numerous studies of episodic long-term memory (LTM) for events have reported activation in ventrolateral (BA 44, 45, 47, and parts of 6), dorsolateral (at or near Brodmann's Areas [BA] 9 and parts of 46), and anterior (BA 10 and parts of 46) PFC. Ventrolateral prefrontal activation has been observed during both LTM encoding and retrieval tasks, whereas dorsolateral and anterior prefrontal activation has been primarily observed during LTM retrieval tasks [9,23,53,67]. Working memory (WM) studies have also reported ventrolateral and dorsolateral prefrontal activation associated with maintenance and manipulation of information across short delays [15,18,29,46,71], with some suggestions that these regions may play differing roles in WM [27,47].

These findings raise two important questions: (1) are the PFC regions that subserve episodic LTM distinct from those that subserve WM? and (2) within LTM or WM, do distinct PFC regions exhibit patterns of activity associated with different task phases (e.g. encoding, maintenance, or retrieval)? Such specificity would argue for characterizing memory systems in terms of familiar task distinctions such as LTM, WM, encoding, and retrieval [58,66]. An alternative approach is to characterize memory systems in terms of component processes—for example, in terms of perceptual (bottom-up or stimulus-driven) and reflective (top-down or internally-generated) processes [30,32]. Within such a framework, reflective processes (e.g. rehearsing information, retrieving information, shifting between task-related features or between tasks, etc.) are the sorts of executive control processes typically linked to prefrontal cortex [40,41,59,63]. These component reflective processes may be flexibly recruited in the service of task goals and not uniquely dedicated to WM or LTM.

Some support for the component process view comes from neuropsychological studies showing that the effect of prefrontal lesions on WM and LTM task performance depends on the reflective complexity of the test. Patients with prefrontal lesions can exhibit intact performance on simple WM span tasks, but impaired performance on WM tasks that tax attentional inhibition or selection processes [17]. Similarly, they can exhibit intact performance on simple LTM

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tests such as recognition or cued recall, but impaired performance on more complex free recall and source memory tests [53,60]. Thus, prefrontal regions may implement reflective processes that are relevant to both WM and LTM [23,30,41,53,61].

Consistent with these findings, results from recent meta-analyses of neuroimaging data also suggest that the same dorsolateral and ventrolateral regions are active during both WM and LTM tasks [9,22]. In contrast, these reviews suggest that anterior regions of PFC may be uniquely activated during LTM retrieval tasks. Based on these results, interpretations of anterior prefrontal activation have largely focused on processes specific to episodic memory retrieval [35,36,67] (but see [11]).

In summary, although recent findings converge on the idea that PFC contributes to memory, it remains unclear whether different regions play roles specific to WM or LTM. This question was recently addressed by four studies, with conflicting results [6,8,43,44]. In one fMRI study by Braver et al. [6], ventrolateral PFC was active during performance of a "2-back" task (used to assess WM), and during blocks of intentional encoding and yes–no recognition trials (used to assess LTM). In contrast, dorsolateral and anterior PFC were selectively active during WM, but not LTM task performance. In another study by Cabeza et al. [8], event-related fMRI was used to compare activity between a delay task requiring memory for the spatial locations of words (used to assess WM) and a "remember-know-new" recognition memory task (used to assess LTM) that was matched for behavioral performance. Contrary to Braver et al., these investigators found that activity in anterior (BA10), dorsolateral (BA 9), and parts of ventrolateral (BA 45,47) PFC was greater during LTM retrieval than during WM trials. Finally, across two experiments, Nyberg et al. [43,44] used positron emission tomography (PET) to examine activity across three separate WM and LTM measures. Across these studies, Nyberg et al. identified areas in left fronto-polar and left ventrolateral PFC that were active during all the memory conditions relative to a non-memory baseline task.

One difficulty in comparing results from previous imaging studies of WM and LTM involves differences in stimulus sets. Most previous imaging studies of WM used small stimulus sets, such that stimuli were repeated from trial-to-trial, whereas most previous LTM studies used large stimulus sets with minimal overlap among items to be remembered. Using a small set of items in the WM but not the LTM task could confound effects related to interference with effects intrinsic to WM and LTM. For example, accumulating proactive interference could increase the degree to which subjects need to evaluate the specific attributes of each item [31], which, in turn, could modulate prefrontal activation [19,28,52,56,57]. Consistent with this view, regions in lateral PFC exhibited greater activation during a 2-back WM task with familiar, repeated scenes than during a 2-back task with novel scenes in another recent study [62].

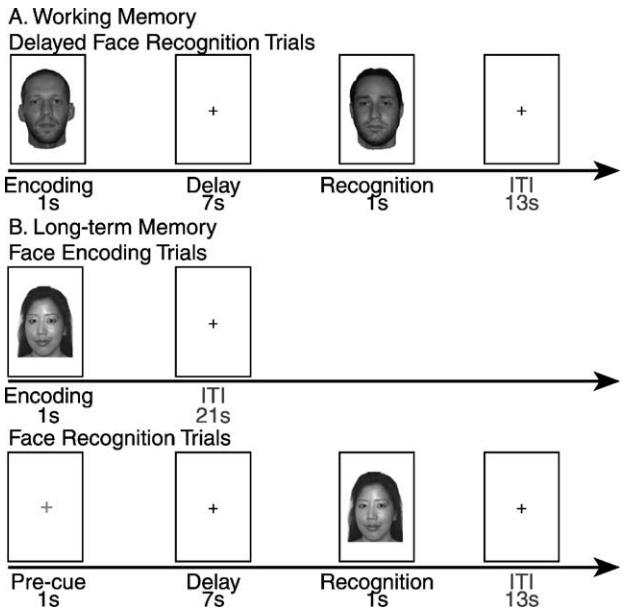

Fig. 1. Schematic depiction of each task. (A) A single trial of the delayed face recognition task used to assess WM. (B) A single trial of the face encoding and recognition tasks used to assess LTM. On each WM and LTM encoding trial, a face to be encoded was presented for 1 s. Similarly, on each WM and LTM recognition trial, a test face was shown after a 7 s delay period. WM trials, however, required the retention of a single face across a 7 s delay, whereas the LTM task required the retention of several faces across several minutes (see Section 2). Thus, activity associated with encoding and recognition could be compared between WM and LTM tasks within the same group of subjects.

Here, using event-related functional magnetic resonance imaging (fMRI) methods to identify temporal patterns of brain activity within a trial [20,48,70], we compared prefrontal activation during WM and LTM tasks. In the present experiment, the stimuli presented during WM trials were novel (i.e. each stimulus was only used on one trial, such that there was no repetition of stimuli across trials), as were the stimuli in the LTM encoding trials. Furthermore, the temporal parameters of each task were matched (see Fig. 1), and the specific stimuli were counterbalanced across WM and LTM trials so that the topography of prefrontal activity associated with encoding and retrieval and WM and LTM could be assessed in the same group of subjects for the same materials.

2. Methods

2.1. Subjects

Five male and three female healthy, right-handed volunteers ranging in age from 19 to 40 were recruited from the University of Pennsylvania student community. All gave full informed consent before participating.

2.2. Procedure

Historically, distinctions between short-term/working memory and episodic long-term memory have focused on

the *amount of information* and the *duration* for which the information is to be remembered [2,3,21]. For example, many WM tasks assess the active maintenance of information that can be retained over the course of a few seconds (usually ranging from one to six items, depending on stimulus complexity), whereas many LTM tasks assess the amount of information that can be retained over longer delays (ranging from several minutes to days), often with distractions interposed between study and test to prevent rehearsal [4,10,21]. Here, the factors of retention duration and amount of information to be learned were used to make the operational distinction between WM and LTM tasks, while holding other variables constant. Specifically, the WM task used in this study required the rehearsal of a single face across a 7 s delay, whereas the LTM task required the retention of several faces across several minutes.

A total of 135 grayscale face stimuli (courtesy N. Kanwisher, MIT) were used in the experiment. Some of these faces had emotional expressions, however, the mapping of stimuli to task (WM versus LTM) was counterbalanced across subjects to control for material-specific effects. To assess WM, participants performed a delayed-recognition task with trial-unique stimuli (see Fig. 1A). In the same session, participants performed intentional encoding and recognition tasks with novel faces, in order to assess encoding and retrieval activation within the context of LTM tasks (see Fig. 1B). On each WM trial, a sample face was shown for 1 s, followed by a fixation cross for 7 s, followed by a probe face for 1 s. A fixation cross was shown on the screen during the 13 s inter-trial interval (ITI). Participants were instructed to pay careful attention to the first face in each trial and maintain a mental image of that face throughout the delay period. Participants were to make a keypress with the left index finger if the second face matched the first (50%) and the right index finger if it did not (50%). On each LTM encoding trial, a face was shown for 1 s, followed by a fixation cross during the 21 s ITI. Participants were instructed to pay attention to each face in order to remember it for a later test. The delay between LTM encoding and recognition testing for any particular item lasted approximately 5–10 min. On each LTM recognition trial, participants were shown a red fixation cross for 1 s, marking the beginning of a trial, followed by a fixation cross for 7 s, followed by a probe face for 1 s. Participants were to make a keypress with the left index finger if the probe face was studied in the previous scanning run (50%) and the right index finger if it was not (50%).

Tasks were administered in alternating scanning runs, such that each run of 18 WM trials was followed by a run of 9 LTM encoding trials, which in turn was followed by a run of 18 LTM recognition trials. Participants performed three runs of each task, for a total of 54 WM and LTM recognition trials and 27 LTM encoding trials. Participants additionally performed a visuomotor response task in order to empirically derive a hemodynamic response function [1] and a passive viewing task to identify face-sensitive regions of extrastriate cortex [33].

2.3. MRI acquisition and processing

Each functional volume consisted of 21 contiguous axial slices acquired with a gradient echo echoplanar sequence (TR = 2000 ms, TE = 50 ms, Matrix size = 64 × 64, slice thickness = 5 mm, FOV = 24 cm) sensitive to blood oxygenation level dependent (BOLD) contrast. fMRI data processing included: sinc interpolation in time to correct for between-slice timing differences in image acquisition [1], motion detection and correction using a six-parameter, rigid-body transformation algorithm provided by Statistical Parametric Mapping (SPM96) software, motion compensation using a partial correlation method [70], and normalization of the time-series of each voxel by its mean signal value to attenuate between-run scaling differences.

2.4. Data analysis

A detailed description of data analysis methods has been presented elsewhere [48,51], and is summarized here. Event-related BOLD responses were analyzed using a modified general linear model [68]. All models incorporated empirically derived estimates of intrinsic temporal autocorrelation [69] and filters to attenuate frequencies above 0.25 Hz and below 0.01 Hz.

Analogous to the way activation is operationally defined in single-unit recording studies, activation during the encoding, delay, and recognition periods of each trial was assessed relative to baseline activity during the ITI [48]. For each subject, BOLD responses during the encoding, delay, and recognition phases in each task were modeled as impulses of neural activity convolved with an individually-derived hemodynamic response function [1,48]. One concern in modeling activity during delay tasks is that neural activity limited to the cue period might produce a hemodynamic response that extends into the subsequent delay period (due to the sluggishness of the hemodynamic response) leading to activity captured by the delay period covariate that is contaminated by cue period activity. However, we have demonstrated that spacing the onset of the delay period covariate at least 4 s from the onset of cue and response covariates successfully identifies delay-specific activity, while activity earlier in the trial is modeled by the cue period covariate [20,48,70]. T statistics were computed from the GLM to assess the magnitude of activation during each trial phase.

Each of the resulting statistical parametric maps (SPMs) were spatially normalized to Montreal Neurological Institute reference brain [12] using algorithms from SPM96 software, and smoothed with a 7.5 mm isotropic Gaussian kernel to account for remaining between-subject anatomical variability. Stereotactic coordinates of peak activations were reported with respect to the Montreal Neurological Institute reference brain [12]. As noted recently by Brett

Table 1
Lateral and anterior prefrontal regions showing BOLD signal increases during the encoding or recognition phase of WM trials or LTM encoding or recognition trials relative to fixation

Region	BA	Encoding								Recognition							
		WM				LTM				WM				LTM			
		x	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)
R. anterior inferior frontal gyrus	47					29	23	−5	10.86	38	19	0	14.75	34	22	−5	7.03
L. anterior inferior frontal gyrus	47	−45	11	−10	5.31	−41	19	−15	8.09	−38	19	−10	7.52	−34	15	5	9.42
R. posterior inferior frontal gyrus	**44/45**									**41**	**26**	**10**	**10.34**	**45**	**26**	**10**	**7.72**
										41	**11**	**25**	**11.26**				
L. posterior inferior frontal gyrus	44/45	−53	8	15	11.39									−53	19	15	7.04
R. precentral sulcus	6/44	45	−8	35	10.48	45	−8	30	10.46	49	4	35	8.71	53	0	35	9.90
L. precentral sulcus	6/44	−53	0	30	6.88	−53	−8	30	8.93	−53	−4	35	11.24	−53	−4	30	6.64
						−49	0	5	11.52	−41	0	15	8.12				
R. posterior middle frontal gyrus	9/46									26	34	30	7.01				
L. posterior middle frontal gyrus	**9/46**									**−49**	**30**	**30**	**14.98**	**−49**	**26**	**20**	**6.97**
R. anterior middle frontal gyrus	10/46									34	45	10	7.60				
L. anterior middle frontal gyrus	**10/46**									**−41**	**52**	**10**	**8.35**				

Note: Regions shown in BOLD were used to define regions of interest for further analyses (see Section 2). R: right, L: left, BA: Brodmann's Area.

et al. [7], the MNI reference brain is not the same size or shape as the brain shown in the Talairach and Tournoux [64] atlas. Software for converting these coordinates to Talairach coordinates is available online (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). However, we should note that the algorithm provided does not always produce coordinates that correspond to those obtained via visual inspection using the Talairach and Tournoux [64] atlas.

Group random-effects analyses were performed for each contrast of interest to test whether the mean of the individual subjects' *t*-values at each voxel was reliably greater than zero. We chose to use *t*-values (instead of parameter estimates) for these analyses because recent work from our group has suggested the presence of scaling effects (affecting both signal and noise components) that vary in magnitude across scanning sessions (Zarahn, unpublished data posted at http://www.voxbo.org/papers/MethodsNote2.pdf). Accordingly, using *t*-statistics (a signal-to-noise measurement) rather than parameter estimates (measuring signal amplitude) as the dependent measure can attenuate these effects. We note that when *t*-values, rather than parameter estimates, are entered into a group analysis, the null hypothesis being tested is that the mean effect size (as opposed to the mean response amplitude) is zero. Nonetheless, virtually identical results were obtained for all comparisons of interest when random-effects analyses were repeated using parameter estimates derived from the GLM.

Areas of significant activation in mapwise analyses were determined by identifying regions whose peak activation exceeded a mapwise threshold of $P < 0.05$ (corrected for multiple comparisons, given the smoothness of the data). The extent of activation surrounding these peaks, used to delineate regions-of-interest (ROIs), was defined as contiguous voxels within the same anatomical region whose significance exceeded $P < 0.001$, uncorrected. Statistical thresholds were one-tailed for contrasts against the ITI, and two-tailed for contrasts between different task conditions.

In addition to analyses of activation differences, a conjunction analysis was performed to assess common regions of activation across WM and LTM trials. For this analysis, random-effects *t*-maps for the encoding and recognition phases of WM trials, and for LTM encoding and LTM recognition trials were thresholded at $P < 0.01$, and voxels surviving this threshold during both WM and LTM trials were identified for each task phase (encoding and retrieval). Thus, the conjunction analysis identified voxels active across both WM and LTM trials with a joint probability of $P < 10^{-4}$.

Although the focus of the present report is on activity within PFC, we additionally report mapwise statistical results for the whole brain for archival purposes. In addition to these mapwise analyses, we also performed ROI analyses to characterize the response properties of three regions—right ventrolateral, left dorsolateral, and left anterior PFC—that appeared to exhibit selective activation during the test phase, particularly on WM trials. ROIs were defined by selecting the extent of contiguously activated voxels surrounding peaks of activation during the test phase of WM trials (see Table 1). Statistical tests on data aggregated for each ROI were evaluated using an uncorrected threshold of $P < 0.05$.

3. Results

3.1. Behavioral results

An ANOVA revealed that participants were significantly more accurate at identifying same ($M = 97.7\%$, S.D. $= 2.8\%$) and different ($M = 97.2\%$, S.D. $= 2.6\%$) faces on WM trials than for studied ($M = 88.9\%$, S.D. $= 7.9\%$) and unstudied ($M = 85.6\%$, S.D. $= 9.9\%$) faces on LTM recognition trials [$F(1, 7) = 13.89$, $P < 0.01$]. Similarly,

mean response times were significantly faster for same (M = 825.9 ms, S.D. = 266.9) and different (M = 785.8 ms, S.D. = 199.8) faces on WM trials than for studied (M = 1433.3 ms, S.D. = 395.3) and unstudied (M = 1494.3 ms, S.D. = 375.1) faces on LTM trials [$F(1, 7) = 49.32$, $P < 0.001$]. No other behavioral effects were statistically significant.

3.2. fMRI results

Group analyses of brain activation during WM and LTM trials relative to the ITI revealed a highly overlapping pattern of activation across the two tasks. Stereotactic coordinates of local maxima of prefrontal activation during encoding and recognition phases of the WM and LTM tasks are listed in Table 1. As shown in Fig. 2A, regions of bilateral ventrolateral PFC along the precentral sulcus (BA 6/44), and inferior frontal gyrus (BA 44, 45, 47) were activated during encoding and recognition phases of both WM and LTM trials. In addition, bilateral dorsolateral (BA 9, 46) prefrontal regions in the posterior middle frontal gyri were activated during the recognition phase of WM and LTM trials. Finally, bilateral anterior (BA 10/46) prefrontal regions in the middle frontal gyrus were activated during the recognition phase of WM trials. During the delay period of WM trials, prefrontal regions in the left anterior inferior frontal gyrus (BA 47; $xyz = -30, 26, -10$; $t(7) = 8.59$), and the right medial frontal gyrus (BA 9; $xyz = 4, 49, 30$; $t(7) = 8.02$) exhibited reliable activation.

To quantify the degree to which similar regions were active during WM and LTM trials, a conjunction analysis was performed (see Section 2). Results of this analysis, shown in Fig. 2B revealed substantial overlap in prefrontal activations across WM and LTM trials. During the encoding phase of WM and LTM trials, overlapping activations were seen in the right and left inferior frontal gyri (BA 44, 45, and 47), and the left posterior middle frontal gyrus (BA 9). During the retrieval phase of WM and LTM trials, overlapping activation were seen in right and left inferior frontal gyri (BA 44, 45, and 47), the right and left posterior middle frontal gyri (BA 9) and left anterior middle frontal gyrus (BA 10/46) and the right superior frontal gyrus (BA 10).

Despite mostly overlapping patterns of activation evoked by the WM and LTM encoding and recognition operations relative to baseline, some PFC regions appeared active in one condition (i.e. WM recognition) and not another (i.e. LTM recognition). However, because such differences could be due to the stringent statistical threshold chosen in our group analysis, direct comparisons between the magnitude of task-related activation between WM and LTM trials were

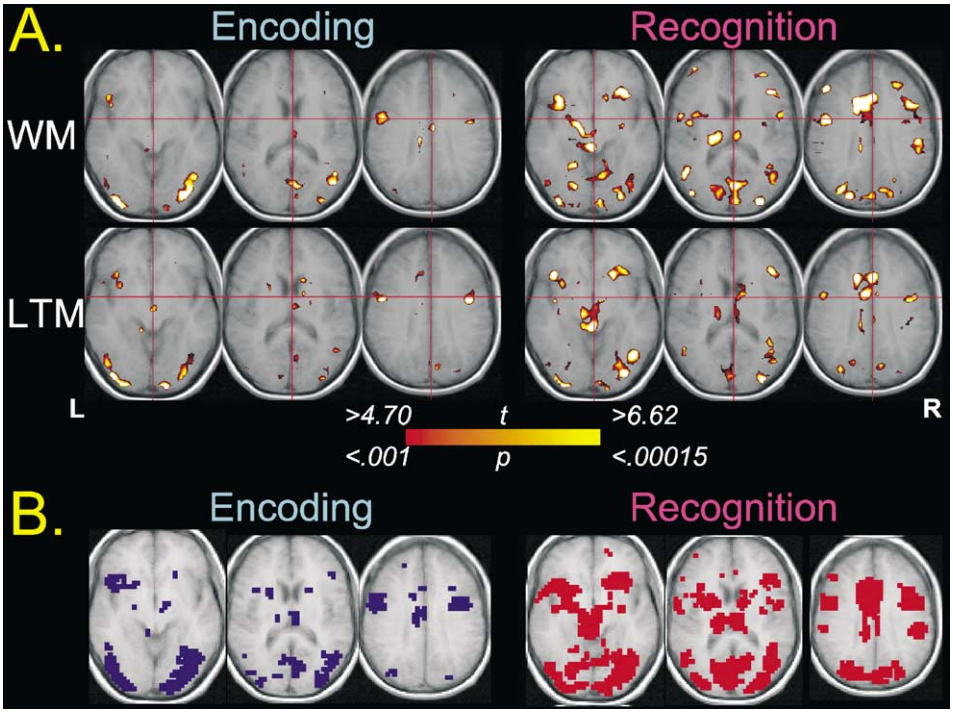

Fig. 2. Prefrontal activation during WM and LTM trials. (A) Results from group analyses are shown for encoding and recognition phases of WM trials (top row) and for LTM encoding and recognition trials (bottom row). Activation maps are overlaid on an average of the spatially normalized anatomical images from the eight participants. Pixels shown in bright yellow met or exceeded a threshold of $t(7) > 6.62$, corresponding to a one-tailed threshold of $P < 0.05$, corrected for multiple comparisons. (B) Results from a conjunction analysis examining overlap in activation during the encoding (left) and recognition (right) phases of WM and LTM trials. Pixels shown in blue (encoding) and in red (recognition) exceeded a joint probability threshold of $P < 10^{-4}$. Note that activations identified in this analysis sometimes extended beyond those shown in the single-condition analyses, because some these voxels identified in the conjunction analysis did not have to exceed the mapwise threshold at the single-condition level.

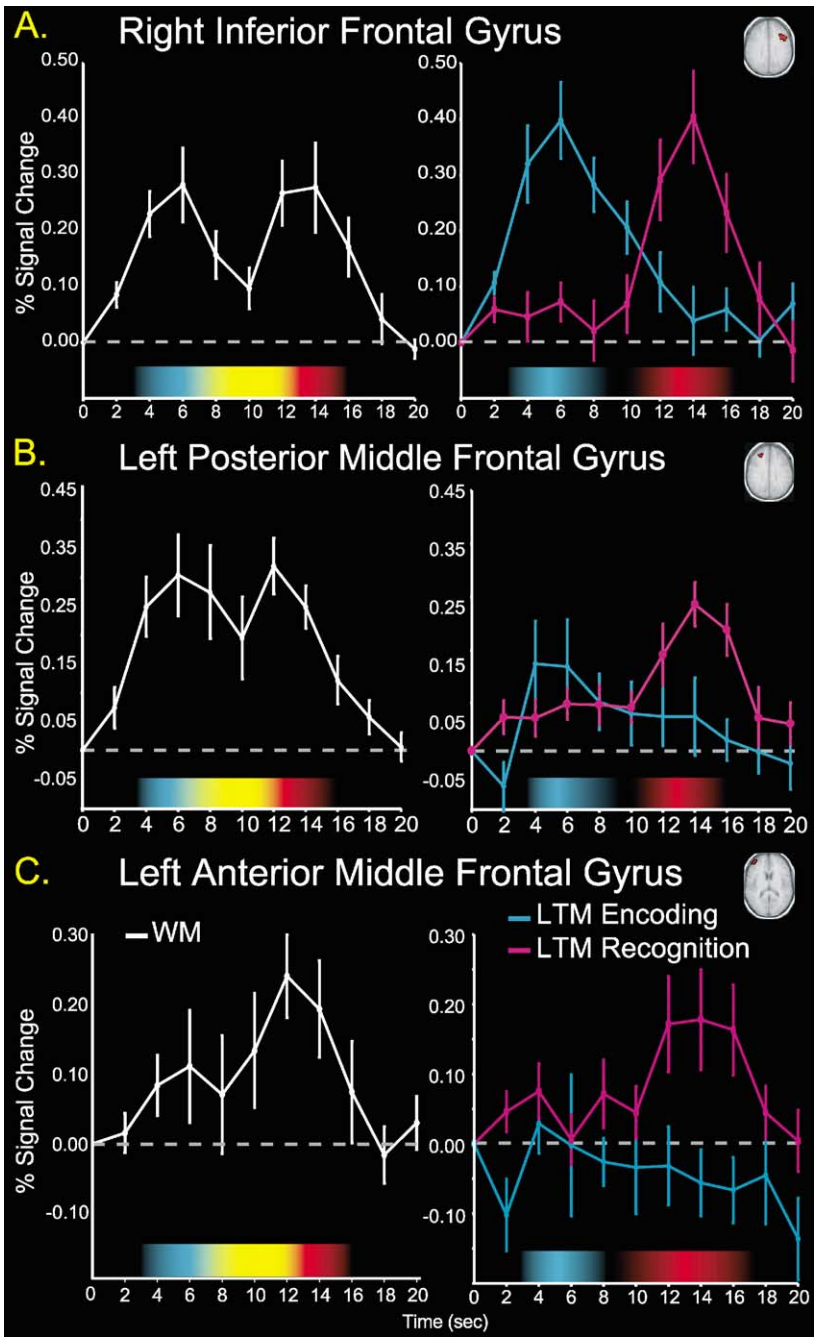

Fig. 3. Temporal dynamics of prefrontal activation during WM and LTM trials. Trial-averaged responses (scaled to a % signal change value relative to trial onset) are shown for ROIs in: (A) right ventrolateral, (B) left dorsolateral, and (C) left anterior PFC. Error bars denote the standard error of the mean across participants. A color gradient shown in the background depicts when responses related to transient encoding (blue), sustained active maintenance (yellow), and transient recognition (red) would be expected to peak, assuming a 4–6 s peak latency for the hemodynamic response [1]. At left, results are shown for WM trials, and at right results are shown for LTM encoding (magenta) and recognition (cyan) trials.

also performed. In these analyses, none of the regions that were active during encoding or recognition in either the WM or LTM tasks showed any significant between-task differences. One small region within left anterior inferior frontal gyrus was more active during LTM recognition trials than during the recognition phase of WM trials (BA 47; $xyz = -34,26,0$; $t(7) = 6.91$). However, this difference must be interpreted cautiously because activity in this region was not reliable relative to baseline on either the recognition phase of WM trials [$t(7) = 1.47$, $P = 0.093$] or on LTM recognition trials [$t(7) < 1$].

To further characterize the nature of prefrontal activity across WM and LTM trials, we examined the temporal dynamics of activity changes in three regions of PFC that

appeared to exhibit selective activation during specific task phases. For example, as shown in Table 1, regions in right ventrolateral (BA 44/45), left dorsolateral (BA 9/46), and left anterior (BA 10/46) PFC appeared to be active during recognition but not encoding, especially during WM trials. Again, activation in these regions was identified using a stringent statistical threshold, leaving open the possibility that these regions might exhibit reliable, but subthreshold activity during other task phases. To characterize the nature of activity in these regions in more detail, we defined ROIs in left dorsolateral, right ventrolateral, and left anterior PFC (see Section 2). Time series data from each subject were trial-averaged within these ROIs and averaged across subjects.

Activation in right ventrolateral PFC, shown in Fig. 3A, increased sharply following stimulus presentation during WM and LTM encoding and recognition trials. Analyses confirmed that activation was significant during the encoding [$t(7) = 5.07$, $P < 0.001$] and recognition [$t(7) = 18.04$, $P < 10^{-6}$] phases of WM trials, and during LTM encoding [$t(7) = 5.78$, $P < 0.0005$] and LTM recognition trials [$t(7) = 5.72$, $P < 0.0005$]. Ventrolateral PFC activation did not reach significance during the delay period of WM trials [$t(7) = 1.01$, $P > 0.10$].

As shown in Fig. 3B, the pattern of activity in left dorsolateral PFC was remarkably similar to ventrolateral PFC. Activation in dorsolateral PFC was significant during the encoding [$t(7) = 3.44$, $P < 0.01$] and recognition [$t(7) = 10.96$, $P < 10^{-5}$] phases of WM trials, and during LTM encoding [$t(7) = 2.59$, $P < 0.05$] and LTM recognition trials [$t(7) = 4.66$, $P < 0.005$] Activation in this region did not reach significance during the delay period of WM trials [$t(7) = 1.29$, $P > 0.10$].

The pattern of responses in the left anterior prefrontal ROI, shown in Fig. 3C, was different than those seen in the dorsolateral and ventrolateral ROIs. Specifically, during WM trials, activity in left anterior PFC gradually increased early in the trial period and sharply increased following the onset of the recognition probe. Analyses confirmed that activation in this region was significant during the recognition phase [$t(7) = 8.98$, $P < 10^{-4}$], but not during the encoding [$t(7) = 1.41$, $P > 0.10$] or delay [$t(7) < 1$] phases of WM trials. Activity in this region significantly increased following presentation of the probe face on LTM recognition trials [$t(7) = 3.44$, $P < 0.01$], but this region showed no reliable increase in activation during LTM encoding trials [$t(7) = 1.05$, $P > 0.15$].

Regions outside of PFC that were active during the encoding and recognition phases of WM and LTM tasks are listed in Tables 2 and 3. These regions included cingulate, parietal, and temporal lobe regions commonly implicated in

Table 2
Regions outside of lateral PFC showing BOLD signal increases during the encoding phase of WM trials and/or LTM encoding trials relative to fixation

Region	BA	WM				LTM			
		x	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)
R. superior frontal gyrus	6					4	−11	60	7.85
L. superior frontal gyrus	8/6					0	8	45	8.18
R. cingulate gyrus	23/24	4	−15	30	8.38				
L. cingulate gyrus	24/32					−4	26	25	6.83
	23/31	−11	−26	30	9.05				
	31	−11	−53	25	7.3				
L. insula						−34	−30	0	8.38
L. inferior parietal lobule	40	−56	−49	50	6.85				
L. parahippocampal gyrus	39/19					−11	−41	−10	7.5
R. lingual gyrus	19	15	−53	−5	7.04				
	18					15	−101	−10	8.42
R. fusiform gyrus	19					30	−64	−15	8.86
L. fusiform gyrus	19					−41	−68	−20	10.87
L. superior temporal gyrus	22	−53	−56	15	7.77				
R. middle temporal gyrus	37/39	49	−64	10	8.06				
L. middle temporal gyrus	37	−45	−64	−25	7.64	−53	−64	5	10.97
L. middle occipital gyrus	19					−49	−71	0	7.49
		−49	−79	−15	7.87	−49	−79	−15	8.79
R. middle occipital gyrus	19	49	−75	5	11.99	38	−86	−15	11.23
R. angular gyrus	39/19					45	−79	25	7.08
L. angular gyrus	39	−38	−83	35	7.06				
R. inferior occipital gyrus	18	34	−86	−10	12.99				
L. inferior occipital gyrus	18					−34	−101	−5	10.46
R. cuneus	18	8	−79	10	7.52				
Thalamus		−4	−34	0	10.94	0	−15	−5	13.15
L. putamen						−23	8	0	9.87
R. caudate nucleus						15	15	5	10.8
						15	0	15	10.22
R. cerebellum						30	−45	−25	8.35

Table 3
Regions outside of lateral PFC showing BOLD signal increases during the recognition phase of WM trials and/or LTM recognition trials relative to fixation

Region	BA	WM				LTM			
		x	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)
R. superior frontal gyrus	8	4	23	30	10.21				
	6	23	−15	60	12.42				
L. superior frontal gyrus	6	−15	−15	55	17.81				
	8/6					−11	11	45	8.26
R. cingulate gyrus	24					8	0	30	6.79
	24/31	8	−30	35	6.78	4	−15	35	9.14
L. cingulate gyrus	24	−15	8	25	13.38	−15	15	30	10.54
		−11	−4	40	14.72	−4	4	45	9.09
	24/31	−11	−34	30	7.28	−11	−34	30	6.86
R. precentral gyrus	4	34	−19	50	12.22	34	−19	60	12.33
		45	−15	50	10.76	45	−11	20	7.46
		56	−8	20	6.95				
	6	56	0	5	8.81	41	−8	35	7.89
L. precentral gyrus	4	−41	−11	15	8.77	−11	−15	60	13.32
		−49	−15	45	11.2	−34	−23	60	7.13
		−34	−19	45	7.18				
		−34	−23	60	9.58				
	6	−60	−4	40	6.77				
		−56	0	5	11.04				
		−45	11	−15	11.07				
R. paracentral lobule	4					15	−30	65	7.3
R. postcentral gyrus	1	41	−38	50	11.94	45	−19	50	11.62
L. postcentral gyrus	1	−49	−30	55	12.96	−49	−30	55	9.77
		−53	−45	50	10.32	56	−38	50	6.79
						−41	−45	60	8.31
						−53	−19	50	11.81
R. insula		45	−15	15	7.91				
L. insula		−38	4	−15	9.81	−41	−8	−10	7.88
		−38	−4	0	9.51				
		−38	−23	0	6.72				
R. inferior parietal lobule	40	30	−49	60	9.23	38	−45	55	10.83
		53	−38	25	8.8				
		53	−30	30	7.42				
L. inferior parietal lobule	40	−41	−56	55	8.45	−41	−53	50	12.3
L. parahippocampal gyrus	27	−11	−34	−5	8.87	−15	−34	0	8.34
R. parahippocampal gyrus	35/12	15	−56	−15	8.38	11	−38	5	7.62
R. superior temporal gyrus	22					45	−49	15	8.18
L. superior temporal gyrus	22	−56	−53	15	7.18				
		−53	11	−5	11.91				
R. middle temporal gyrus	37					53	−60	10	6.93
	37					45	−64	5	6.85
	39					49	−75	15	8.61
L. middle temporal gyrus	37	−53	−64	10	9.35	−49	−68	5	12.03
	39					−49	−75	−15	6.88
R. fusiform gyrus	37/19					34	−64	−20	7.4
L. fusiform gyrus	37	−45	−49	−25	7.36				
	19	−49	−75	−20	8.39				
R. precuneus	18	15	−79	25	7.17	11	−79	30	6.68
	7	8	−68	55	8.97				
		23	−79	50	12.97				
L. precuneus	7	−19	−83	45	9.69				
	18					−19	−79	25	7.88
L. lingual gyrus	19	−23	−56	−10	7.46				
		−23	−45	0	7.68				
	19/30	−19	−79	−10	8.33	−4	−79	−20	6.68
R. lingual gyrus	18/36	23	−83	−15	6.88				
	19	23	−53	0	12.42				
		11	−68	−10	6.78	26	−71	−15	10.68
R. superior occipital gyrus	19	34	−90	25	7.66				
L. superior occipital gyrus	19/4	−34	−83	35	11.52	−34	−83	25	9.92

Table 3 (*Continued*)

Region	BA	WM				LTM			
		x	*y*	*z*	*t*(7)	*x*	*y*	*z*	*t*(7)
R. middle occipital gyrus	19	41	−79	−15	6.97	45	−68	−10	9.33
		49	−68	5	10.66				
	19/39	30	−94	10	11.6	34	−94	10	11.26
L. middle occipital gyrus	18	−41	−90	0	12.86				
		−23	−94	20	11.89				
L. inferior occipital gyrus	18	−38	−94	−10	10.93	−41	−94	−10	7.81
	19					−30	−86	−20	8.39
						−26	−101	−5	12.514
R. inferior occipital gyrus	18	30	−90	−10	7.9	34	−83	−5	14.14
L. cuneus	17	−8	−67	5	7.75				
	18	−26	−86	25	13.3	−19	−98	20	7.55
	19	−8	−90	25	7.39				
R. cuneus	17	4	−79	5	9.87				
		4	−94	10	7.28	8	−94	15	7.72
		8	−94	−10	7.48	19	−101	0	6.88
	18	26	−75	25	8.68				
L. caudate nucleus						−15	−19	15	6.99
R. caudate nucleus						11	15	−5	7.4
L. putamen						−23	4	0	10.61
R. putamen		26	11	0	8.27				
		30	−19	−5	7.74				
		19	0	0	7.44				
Thalamus		8	−23	10	6.77	8	−8	−5	11.99
		−15	−11	−10	8.22				
		−23	−26	10	8.12				
Superior colliculus		0	−38	−10	10.35				
Cerebellum		−8	−41	−20	9.66				
		−30	−64	−25	9.02	−34	−64	−25	9.87

Note: R: right, L: left, BA: Brodmann's Area.

both WM and LTM tasks [9]. In addition, regions in the right ($x = 30$, $y = -22$, $z = -15$, $t(7) = 14.89$) and left ($x = -30$, $y = -15$, $z = -20$, $t(7) = 7.34$) anterior hippocampus and the left superior temporal gyrus (BA 22; $xyz = -68, -23, -10$; $t(7) = 6.78$) were active during the delay period of the WM task. A detailed description of results from medial temporal regions has been previously published [51]. Comparisons between WM and LTM trials revealed that a region in the left fusiform gyrus (BA 19; $x = -26$, $y = -56$, $z = -20$; $t(7) = 9.59$) was more active during LTM encoding trials than during the encoding phase of WM trials. In addition, regions in the left (BA 4; $x = -53$, $y = -11$, $z = 50$; $t(7) = 8.27$) and right (BA 6; $x = 26$, $y = -15$, $z = 60$; $t(7) = 9.60$) precentral gyri were more active during the encoding phase of WM trials than during LTM encoding trials. Finally, regions in the left superior temporal sulcus (BA 22; $x = -68$, $y = -49$, $z = 15$; $t(7) = 7.33$) and the left inferior parietal lobule (BA 40; $x = -64$, $y = -41$, $z = 40$; $t(7) = 8.00$) were more active during the recognition phase of WM trials than during LTM recognition trials.

In summary, results from analyses of PFC activation revealed two major findings: First, common regions of dorsolateral, ventrolateral, and anterior PFC were activated during both WM and LTM tasks. Second, whereas regions of dorsolateral and ventrolateral PFC were activated during both encoding and recognition phases of each task, left anterior PFC was reliably activated only during the recognition period of the WM and LTM tasks.

4. Discussion

In the present study, we used event-related fMRI to identify the degree to which distinct prefrontal regions support performance during different phases of WM and LTM tasks. Our results revealed a remarkable degree of overlap between activated prefrontal regions during WM and LTM trials. Thus, the present findings cast doubt on the idea that any of these prefrontal regions is uniquely recruited to support either WM or LTM. Instead, the present results converge with neuropsychological [53,61] evidence from humans, and neurophysiological evidence from non-human primates [49,50] suggesting that prefrontal regions implement processes that support both WM and LTM task performance [30,41].

Two previous fMRI studies [6,8] obtained evidence of differential prefrontal activation between WM and LTM tasks, although different patterns of results were observed

across these studies. Several factors could have contributed to the relative absence of differential prefrontal activation between WM and LTM, in the present study compared to prior studies [6,8]. For example, because the sample size in the present study was smaller than those used in the studies by Cabeza et al. and Braver et al., we may have lacked sufficient statistical power to detect subtle differences between the conditions. Furthermore, task difficulty (as indexed by RT and accuracy measures) was not equated between WM and LTM trials, and it is possible that this may have masked true activity differences between the conditions [8]. Obviously, these concerns preclude the interpretation that prefrontal activity is insensitive to differences between WM and LTM tasks. Nonetheless, the present results showed that overlapping regions in anterior, ventrolateral, and dorsolateral PFC were consistently active across both WM and LTM trials when stimuli and trial structure were equated. Accordingly, this positive finding suggests that task-related differences reported in other studies do not necessarily reflect qualitative differences in prefrontal contributions to different types of memory tasks.

The prefrontal activity differences reported by Braver et al. [6] and Cabeza et al. [8] may have reflected differences in the degree of reflective processing engaged by the specific WM and LTM tasks used in the two experiments. For example, the 2-back (WM) and the yes-no recognition (LTM) tasks used by Braver et al. [6] varied in the degree to which trial-to-trial updating is required, and the delay (WM) and the remember-know (LTM) tasks used by Cabeza et al. [8] varied in the degree to which subjects were required to reflect upon episodic detail associated with test probes. Thus, the results of Cabeza et al. [8] and Braver et al. [6], along with the present results, may indicate that prefrontal activity is sensitive to the reflective demands of a particular memory task, irrespective of whether the task requires reference to currently active (WM) or inactive (LTM) representations [30,41].

These results are in agreement with accounts of prefrontal function that emphasize its role in processes that are involved in both working memory and episodic long-term memory [45,49,53], however, the specific nature of these processes remains unresolved. One hypothesis proposed by several researchers is that lateral prefrontal regions may be critical for implementing top-down attentional modulation of posterior cortical activity that enables transient attentional selection and inhibition [13,14,16,34,49,61], long-term memory retrieval [26,50,65], as well as sustained maintenance [24,25] in the face of distraction. Indeed, extant evidence indicates that PFC may modulate posterior cortical activity as early as 100 ms following presentation of a visual stimulus [5,50].

Although results from this study did not support the idea that any frontal regions play a role specific to WM or LTM, we did observe subtle differences in response properties between different prefrontal regions. Specifically, results showed that areas of ventrolateral (BA 44, 45, 47), dorsolateral (BA 9, 46), and right anterior PFC exhibited transient peaks of activation following stimulus presentation during WM and LTM trials. In contrast, left anterior PFC (BA 10/46), exhibited robust activation during the decision phase of the WM and LTM tasks, but did not exhibit reliable activation during stimulus encoding phases of these tasks. Activation in left anterior PFC was therefore driven by the demand to make a memory decision, whereas activation in lateral PFC was driven by the presentation of a task-relevant object.

The fact that left anterior PFC was not reliably active during stimulus encoding may simply reflect a null result due to insufficient statistical power. Nonetheless, strikingly similar results were reported by Cabeza et al. [8]. As in the present study (see Fig. 3C), Cabeza et al. [8] observed that anterior prefrontal activity progressively increased as subjects anticipated a cue to make a recognition decision. These findings led Cabeza et al. to conclude that anterior PFC participates in the establishment of a neurocognitive set to retrieve episodic information, or an "episodic retrieval mode" (cf. [35]).

These results are consistent with accumulating evidence that anterior PFC may implement different processes than more posterior lateral prefrontal regions [9,11,22]. As noted earlier, previous studies have shown that anterior PFC is active during episodic retrieval tasks and reliably more active during retrieval than encoding [35–37]. Furthermore, activation in this region was greater during source memory tasks than during yes–no recognition tasks [42,52,56,57]. All of these findings suggest that left anterior PFC is recruited under conditions when a memory attribution is required.

Some clues to the functional significance of left anterior PFC activity during episodic retrieval come from a previous event-related fMRI study, in which we examined prefrontal responses during item and source memory tests [52]. Regions in dorsolateral and ventrolateral PFC were activated during both encoding and recognition of objects, but increasing the specificity of information to be retrieved did not modulate activity in these regions. Left anterior PFC was reliably active during retrieval, and activation in this region increased with demands to retrieve perceptually detailed information about studied objects. These modulations were observed for studied and unstudied objects, and results from parallel electrophysiological studies suggest that they occurred as early as 200 ms following stimulus onset [54,55]. Because differences were seen for both old and new objects, it was unlikely that activation in this region solely reflected retrieval of learned information. Instead, these and other results [56] suggest that left anterior PFC was implementing processes critical for the "on-line" monitoring and evaluation of specific memory characteristics during retrieval. These findings suggest that anterior PFC may implement processes critical for the evaluation of information in comparison with active memory [11,52,54,55].

In conclusion, results from this study suggest that different regions of PFC may implement complementary functions that are engaged across WM and LTM tasks. These

results suggest that the neural organization of particular prefrontal regions may not directly correspond to system-level distinctions between WM and LTM, but rather to distinctions among component processes recruited during these and other mental activities [30,32]. Although this view may seem to disagree with theories that propose distinct memory systems for WM and LTM, we note that a full understanding of the function of a given prefrontal region may require understanding of its interactions with other regions [38,39,43,44]. Indeed, it is likely that similar prefrontal regions may contribute to both WM and LTM, but that it is the particular pattern and timing of interactions among these and other regions that differentiates these forms of memory.

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