

Direct Comparison of Prefrontal Cortex Regions Engaged by Working and Long-Term Memory Tasks

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Received February 23, 2000

Neuroimaging studies have suggested the involvement of ventrolateral, dorsolateral, and frontopolar prefrontal cortex (PFC) regions in both working (WM) and long-term memory (LTM). The current study used functional magnetic resonance imaging (fMRI) to directly compare whether these PFC regions show selective activation associated with one memory domain. In a within-subjects design, subjects performed the *n*-back WM task (two-back condition) as well as LTM encoding (intentional memorization) and retrieval (yes–no recognition) tasks. Additionally, each task was performed with two different types of stimulus materials (familiar words, unfamiliar faces) in order to determine the influence of material-type vs task-type. A bilateral region of dorsolateral PFC (DL-PFC; BA 46/9) was found to be selectively activated during the two-back condition, consistent with a hypothesized role for this region in active maintenance and/or manipulation of information in WM. Left frontopolar PFC (FP-PFC) was also found to be selectively engaged during the two-back. Although FP-PFC activity has been previously associated with retrieval from LTM, no frontopolar regions were found to be selectively engaged by retrieval. Finally, lateralized ventrolateral PFC (VL-PFC) regions were found to be selectively engaged by material-type, but uninfluenced by task-type. These results highlight the importance of examining PFC activity across multiple memory domains, both for functionally differentiating PFC regions (e.g., task-selectivity vs material-selectivity in DL-PFC and VL-PFC) and for testing the applicability of memory domain-specific theories (e.g., FP-PFC in LTM retrieval). © 2001 Academic Press

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INTRODUCTION

A growing neuroimaging literature has highlighted the role of the prefrontal cortex (PFC) in both working memory (WM) and long-term memory (LTM). However, the literatures on each of these memory domains have largely remained separate. A few investigators have noted the presence of specific PFC regions that appear to be activated in both WM and LTM tasks (Buckner and Koutsal, 1998; Wagner, 1999). However, the relationship between PFC activity in WM and LTM has not yet been explored directly. In particular, it is not known whether specific PFC regions are preferentially engaged by WM or LTM tasks. In the current study, we examine this question using functional magnetic resonance imaging (fMRI) to probe brain activity during the performance of both WM and LTM tasks using both verbal and nonverbal stimulus materials.

The PFC has long been thought to play a central role in WM function. Neuropsychological studies have demonstrated that patients with PFC lesions show impairments on tasks involving WM, such as the self-ordered pointing task (Petrides and Milner, 1982). Neurophysiological studies with behaving primates have provided more direct evidence of PFC involvement in WM, by demonstrating sustained, stimulus-specific activity during the delay periods of simple WM tasks, such as the delayed response paradigm (Fuster, 1989; Goldman-Rakic, 1987). In the last decade, functional neuroimaging studies have provided a means by which to examine the neural basis of WM in healthy humans. Numerous neuroimaging studies have now extended the findings from the animal and neuropsychological literature, by demonstrating activity in several PFC regions during a wide range of WM tasks (Cabeza and Nyberg, 2000; D'Esposito *et al.*, 1998; Owen, 1997;

Smith and Jonides, 1999). More recently, neuroimaging research has also suggested that PFC, in particular dorsolateral PFC (DL-PFC) regions, may be specifically involved in active maintenance functions, by demonstrating that in these regions, activity: (1) increases as the duration of the maintenance interval increases (Barch *et al.*, 1997; Braver and Cohen, in press); and (2) is sustained across the duration of the maintenance interval (Cohen *et al.*, 1997; Courtney *et al.*, 1997). Recent reviews of the literature have also suggested that DL-PFC activity during WM tasks might instead reflect more "executive" aspects of WM function, including the monitoring and manipulation of actively maintained information (D'Esposito *et al.*, 1998; Owen, 1997; Smith and Jonides, 1999).

Neuropsychological and neuroimaging studies have also demonstrated an important role for PFC in LTM processes. Patients with PFC damage show impairments in the strategic utilization of memory (Janowsky and Shimamura, 1989; Schacter, 1987; Shimamura, 1995). Prominent deficits have been observed in domains such as free recall, proactive interference, temporal-order memory, and source memory (Shimamura, 1995). With the advent of functional neuroimaging methods, there has been an explosion of studies which have focused on the role of PFC involvement in LTM. An important outcome of this research is the finding that specific PFC regions are reliably engaged by a variety of LTM tasks (Buckner and Koutstaal, 1998). For example, studies of LTM encoding have reliably activated ventrolateral PFC (VL-PFC) regions (Buckner, 1996). Moreover, in recent work it has been demonstrated that the degree of activity in these VL-PFC regions during encoding can be used to predict, on average, the probability that those materials will later be successfully recalled (Brewer *et al.*, 1998; Wagner *et al.*, 1998c). In contrast, studies of LTM retrieval have highlighted the reliable presence of activity in more anterior, frontopolar PFC (FP-PFC) regions (Buckner, 1996; Buckner and Koutstaal, 1998; Cabeza and Nyberg, 2000; Nyberg *et al.*, 1996). Recent studies have focused on the functional role of FP-PFC activity during retrieval, such as examining whether the activity is best reflects retrieval mode, retrieval effort, or retrieval success (Buckner *et al.*, 1998; Rugg *et al.*, 1996; Wagner *et al.*, 1998a).

Given the prominence of PFC activity in both WM and LTM neuroimaging studies, it is somewhat surprising that the literatures on each of these memory domains have proceeded largely in isolation of the other. As a result, interpretations of PFC activity have largely remained domain-specific. However, it is not clear whether these domain-specific interpretations are truly warranted. For example, although activation in anterior or frontopolar regions of PFC have been taken to be a marker of processes associated with LTM retrieval (Buckner and Koutstaal, 1998), FP-PFC acti-

vation has sometimes been observed during performance of complex WM tasks (Christoff and Gabrieli, 2000; MacLeod *et al.*, 1998). Likewise, activation in DL-PFC has typically been associated with active maintenance processes in WM (Barch *et al.*, 1997; Cohen *et al.*, 1997). Although activation in this region is not typically observed during LTM encoding, there have been reports of DL-PFC activity during retrieval (Buckner, 1996; Wagner *et al.*, 1998a). Thus, it is currently not clear whether FP-PFC and DL-PFC regions are actually preferentially activated during WM and LTM tasks.

Another issue that has been addressed separately within the neuroimaging literatures on WM and LTM is that of material-specificity within PFC. Interestingly, the findings from each of these literatures may be somewhat conflicting. In particular, within the neuroimaging literature on LTM, material-specific lateralization has recently been observed during episodic encoding (Kelley *et al.*, 1998; Klingberg and Roland, 1998; Wagner *et al.*, 1998b). For example, Kelley *et al.* (1998) observed a within-subjects double dissociation in PFC activity during intentional memorization of familiar words, nameable pictures, and unfamiliar faces. Selective left PFC activity was observed during encoding of words, and selective right PFC activity was observed during encoding of faces. Activity was bilateral during encoding of nameable pictures. This same pattern of asymmetry for encoding of verbal vs. non-verbal materials has also been extended to retrieval as well as encoding (McDermott *et al.*, 1999a; Wagner *et al.*, 1998b). In the WM literature, the question of material-related specialization has been motivated by a prominent cognitive psychological model, which postulates the existence of separate, material-specific memory buffers for both verbal/phonological and visual/spatial information (Baddeley, 1986). There have been a number of neuroimaging studies that have directly investigated whether such material-specificity exists within PFC regions engaged by WM tasks. However, the results from these studies have been mixed, with some studies finding material-specificity (Smith and Jonides, 1997) and others not (D'Esposito *et al.*, 1998; Nystrom *et al.*, 2000; Owen *et al.*, 1998). Results from meta-analyses and reviews of the literature appear to suggest that material-related specialization seems to be most reliable within VL-PFC regions (D'Esposito *et al.*, 1998; Smith and Jonides, 1999). However, it remains an open question as to whether material-effects are memory-selective or instead generalize across different memory domains (i.e., WM vs LTM).

In the current study, we directly compare brain activity during WM and LTM tasks, by using a within-subjects repeated-measures design. We focus specifically on PFC, as this region has received the most attention in neuroimaging studies of memory. We examined WM using the *n*-back paradigm, as it has been

extensively studied in neuroimaging research (e.g., Braver *et al.*, 1997) and reliably engages different PFC regions. The task requires subjects to view a sequence of regularly presented items and indicate when the currently viewed item is identical to an item presented n trials back, where n is specified by the experimenter prior to the sequence. Additionally, we examined LTM during both encoding and retrieval phases. During encoding, subjects intentionally attempted to memorize a sequence of regularly presented items. During retrieval, subjects viewed a sequence of items and made yes/no recognition judgments about whether they had viewed each item previously during the experiment. Finally, we examined the effect of performing each task with different stimulus materials. Two conditions of each memory task were performed, one using familiar visual words, and the other with unfamiliar faces. These different material types were chosen in order to maximize differences in the processing strategies adopted by subjects. Familiar word stimuli were expected to elicit verbally biased processing strategies, whereas unfamiliar faces were expected to elicit non-verbally biased strategies.

The experimental design allowed us to test a number of theoretical hypotheses. First, we predicted that we would observe activity in DL-PFC regions that was selective to WM. This prediction was based on the hypothesis that DL-PFC is critically important for tasks requiring active maintenance over intervening items and/or the monitoring and manipulation of maintained information (Cohen *et al.*, 1997; Postle and D'Esposito, 2000). The n -back task requires that items stored in WM are maintained both in terms of their identity and temporal order, with this information being updated on a trial-to-trial basis. DL-PFC regions responsible for these functions should not be engaged during the LTM tasks, because they make no such requirement for temporal ordering and sustained maintenance. Our second prediction was that we would observe activity in FP-PFC regions that was selective to LTM retrieval. This prediction was based on the hypothesis that FP-PFC activity reflects an episodic retrieval "mode," that is dependent upon task demands (Cabeza and Nyberg, 2000; Lepage *et al.*, 2000). The recognition condition is expected to elicit such a mode based on the explicit instructions for subjects to determine whether they remember seeing each item previously. Such a retrieval mode is not expected to be elicited during LTM encoding and is likely not to be present during WM either, unless subjects go against task instructions, and spontaneously adopt a retrieval strategy rather than using WM for making response decisions. Our final prediction was that we would observe evidence of material-specificity within lateralized VL-PFC regions, with verbal materials activating left hemisphere regions and non-verbal materials activating right hemisphere regions (Kelley *et al.*, 1998).

Moreover, we predicted that this pattern of lateralized activity would be equally present in all three memory tasks. We based this prediction on the hypothesis that material-effects in PFC are not tied to the demands of a particular memory domain, but instead reflect the task-driven extraction of higher-order, material-specific representational features from each item (McDermott *et al.*, 1999a).

METHODS

Subjects. Twenty-eight neurologically normal right-handed subjects participated in this study. Subjects were 14 males and 14 females, with a mean age of 36.5 years. Subjects were paid \$25 for each hour of participation, and gave informed consent in accordance with guidelines set by the Human Studies Committee at Washington University.

Behavioral tasks. Subjects performed a working memory task and long-term memory encoding and retrieval tasks. The working memory task was the two-back condition of the n -back paradigm, adapted from Braver *et al.* (1997). In this task, subjects monitor for target events, which occur whenever the currently presented item is identical to the one presented two trials back. The encoding task required intentional memorization of items and was adapted from Kelley *et al.* (1998). The retrieval task was similar to one performed by McDermott *et al.* (1999a) and required recognition judgments regarding whether presented items had previously been seen in the experiment, either in the working memory or encoding conditions. Two conditions of each task were performed, which varied only by the type of stimulus materials used: words or faces.

Stimulus presentation parameters in all task conditions were set up as similarly as possible to facilitate cross-condition comparisons. All stimuli were presented centrally on a visual display. Words were 3–10 letters in length (subtending $\sim 0.5^\circ$ of visual angle) and presented in 24-point Geneva font. Faces were taken from a database created by N. Cohen and colleagues (Althoff and Cohen, 1999) and initially used in the Kelley *et al.* (1998) study. Face stimuli subtended $\sim 6^\circ$ of visual angle vertically and horizontally. Conditions were performed in scanning runs lasting 255 s and were comprised of alternating "task" and "fixation" blocks. Each task block lasted 40 s, and each fixation block lasted 25 s. Seven blocks total were presented in each run (4 task, 3 fixation). In each task block, 16 items were presented (2000 ms stimulus duration, 500 ms interstimulus interval).

During two-back task blocks, subjects were instructed to press one button with their right-hand on a hand-held response box for targets and another button for nontargets. Targets occurred with 33% frequency, and nontarget repeated stimuli (i.e., 1-back or 3-back repeats) occurred occasionally as foils. During encod-

ing task blocks, subjects were instructed to pay careful attention to each item for a later memory test. To control for motor responding, subjects were instructed to press both buttons together upon the offset of each stimulus. During retrieval task blocks, subjects were instructed to press one button with their right-hand on a hand-held response box for old (i.e., previously seen) items and another button for new items. Old and new items occurred in a randomly mixed fashion with 50% frequency each. Half of the old items had been initially presented during the encoding task, and half were presented during the two-back task. During fixation blocks, subjects were instructed to maintain fixation on a centrally presented cross-hair.

Six runs total were performed by each subject. Within an individual run, only one type of task was performed (two-back, encoding or retrieval) and only one type of stimulus was presented (words or faces) during all of the task blocks. The order of material-type and memory conditions were counterbalanced across subjects, with the following two constraints: (1) all memory tasks with a specific stimulus type (word or face) were performed in a row before switching to the other stimulus type; and (2) the retrieval task was always presented as the last of the three memory tasks for a particular stimulus type. Furthermore, stimulus sequences for the encoding and two-back tasks were counterbalanced across pairs of subjects, such that the two-back sequence for one subject of the pair was the encoding sequence for the other subject of the pair and vice versa.

Functional imaging. Images were acquired with a 1.5 T Siemens Vision whole body scanner. Functional images were acquired using an asymmetric spin-echo echoplanar sequence (TR = 2500 ms, TE = 50 ms, flip = 90°). During each functional scanning run 102 sets of 16 contiguous, 8-mm-thick axial images were acquired parallel to the anterior–posterior commissure plane (3.75 × 3.75 mm in-plane resolution), allowing complete brain coverage at a high signal-to-noise ratio (Conturo *et al.*, 1996). Structural images were acquired using a high resolution (1.25 × 1 × 1 mm) sagittal 3-D MP-RAGE (Mugler and Brookeman, 1990) T1-weighted sequence (TR = 9.7 ms, TE = 4 ms, flip = 12°, IT = 300 ms).

Visual stimuli were generated using an Apple Power Macintosh computer running PsyScope software (Cohen *et al.*, 1993). Stimuli were projected to subjects with an AmPro LCD projector (model 150) onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button Box was used to record subjects' behavioral performance. A thermoplastic face mask was used to minimize head movement.

Data analysis. Behavioral performance data were

analyzed for both the two-back and recognition tests by conducting ANOVAs on accuracy and RT measures. Functional imaging data were analyzed according to the following procedures. All functional images were first corrected for movement using a rigid-body rotation and translation correction (Friston *et al.*, 1996; Snyder, 1996), and then registered to the subject's anatomical images (in order to correct for movement between the anatomical and function scans). The data were then scaled to achieve a whole-brain mode signal value (used in place of mean because of its reduced sensitivity to variation in brain margin definition) of 1000 for each scanning run. This normalization procedure was conducted on a run-by-run basis (rather than image-by-image) to reduce the effect of between-run scanner drift or instability without affecting within run signal-changes. The data were then spatially smoothed with an 8-mm FWHM Gaussian kernel. Subjects' structural images were transformed into standardized atlas space (Talairach and Tournoux, 1988), using a 12-dimensional affine transformation (Woods *et al.*, 1992; Woods *et al.*, 1998). The functional images were then registered to the reference brain using the alignment parameters derived for the structural scans.

Group analyses were conducted using a voxelwise random-effects model with subject serving as the random effect. In order to control for linear drift during and between scanning runs, mean difference images were first computed for each run by subtracting activity during fixation blocks from activity during task blocks. All analyses were then conducted on these mean difference images. To protect against false positive activations, in all analyses an identified region was only considered to be significant if it both passed the statistical criteria, described below, and occurred within a cluster of eight or more contiguous voxels. Finally, to increase interpretability, only positive activations were considered in these analyses.

Two types of primary analysis were conducted: (1) a test for task-selectivity; and (2) a test for material-selectivity. In order to ensure that selectivity was based on stringent criteria, both analyses subjected the data to multiple statistical tests (both *t* tests and ANOVAs), each set with an image-wise significance threshold at $P < 0.05$. Regions were identified only if they simultaneously passed all tests. To be identified as task-selective, a region had to pass the following tests: (1) significant activation during runs involving the preferred memory task (collapsing across material-type); and (2) significantly greater activity for the preferred task when compared to either of the nonpreferred tasks. Additionally, voxels were masked out of task-selective regions if they passed either of the following tests: (1) a significant activation response during runs involving either of the non-preferred memory tasks; or (2) a significant task × material interaction. To be identified as material-selective, a region had to pass

the following tests: (1) a significant activation response during runs involving the preferred material-type (collapsing across tasks); and (2) significantly greater activity for the preferred material than the non-preferred material. Additionally, voxels were masked out of material-selective regions if they passed either of the following tests: (1) a significant activation response during runs involving the non-preferred material-type; or (2) a significant task \times material interaction. Following the primary analyses, region-of-interest (ROI) analyses were then conducted to examine the main effect of task-type in the material-selective regions, and the main effect of material-type in the task-selective regions. For the ROI analyses, data were expressed as percentage change relative to fixation.

RESULTS

Behavioral Data

During performance of the two-back task, subjects averaged 89% accuracy (84% hits, 9% false alarms). A *t* test conducted to examine the effects of material type revealed no significant differences in accuracy between words and faces ($t(27) = 1.42$, $P > 0.1$). However, subjects were significantly faster at responding to words than faces (face RT: 1043 ms; word RT = 916 ms; $t(27) = 3.5$, $P = 0.002$).

Performance on the recognition task determined the degree to which items were successfully encoded. Previously studied items from both the intentional encoding and two-back tasks were included (in a randomly intermixed fashion) in the test. Due to technical difficulties, recognition data from two subjects were corrupted and consequently were not analyzed. Overall, recognition performance (expressed as percentage correct) was 74% (68% hits, 20% false alarms). An ANOVA was conducted on previously studied items, including study task (intentional encoding vs two-back) and material-type (word, face) as factors. This analysis revealed no main effects of either factor ($F < 1$). However the task \times material interaction was marginally significant ($F(1,25) = 3.77$, $P = 0.06$). This was due to recognition for faces being slightly better for faces seen during the two-back task (face recognition: two-back = 70%, encoding = 67%), but recognition for words being slightly better for words seen during the intentional encoding task (word recognition: two-back = 64%, encoding = 72%). Additionally, when considering new items only, significantly more false alarms were made for faces than words (face = 29%, word = 12%; $t(25) = 4.25$, $P < 0.001$).

Imaging Data

Two different analyses of the imaging data were conducted, one testing for task-selectivity and the

other testing for material-selectivity. Although we collected whole-brain imaging data, our focus was on activated regions within PFC, and only those are reported. Data from nonfrontal regions are available upon request from the author and will be the subject of a later report. The results of both analyses are summarized in Table 1 and described in detail below.

Task-selective regions. A number of prefrontal regions were found to show task-selective patterns of activity (see Fig. 1). The majority of these regions were found to be selectively activated in the two-back working memory task. Most prominent among these were bilateral regions of activity in DL-PFC (BA 46/9). A frontopolar PFC region in the left hemisphere (BA 10) was also observed to show a selective response in the two-back task. ROI analyses indicated that all of the working memory selective regions were equally activated by both material types, as indicated by nonsignificant main effects of material in ANOVA tests (all $P > 0.1$; see Fig. 1). Two prefrontal regions were also identified that were selectively activated during encoding, a left ventrolateral region (BA 45) and a right medial frontopolar region (BA 10). ROI analyses revealed that both regions also showed significant main effects ($P < 0.05$) of material type (i.e., when collapsed across tasks; see Fig. 1). The left hemisphere region was found to be more activated by words, while the right hemisphere region was found to be more activated by faces.

Based on our stringent criteria, there were no retrieval-selective regions identified. However, when the size criteria was removed as part of an exploratory analysis, a small (four voxel) retrieval-selective region was identified in the right hemisphere within the frontal operculum/anterior insula. Because we had predicted that we would observe retrieval-selective regions in the FP-PFC, we conducted additional exploratory analyses of this region to better understand the pattern of activity occurring there. Specifically, we determined that there were frontopolar regions significantly activated during retrieval (compared to fixation). Moreover, we also identified a number of voxels within right frontopolar cortex, which showed significantly greater activity in retrieval relative to encoding. These results replicate previous findings (McDermott *et al.*, 1999a,b). However, in all of these voxels, there was no greater activity (even using very liberal statistical criteria) during retrieval when compared to the two-back task. These results suggest that our failure to identify any retrieval-selective regions in right-FP-PFC was not due to an overly stringent criteria.

Material-specific regions. Prefrontal regions were identified which showed either specificity for words or faces. These regions were primarily hemispherically lateralized, with word-specific regions located in the

TABLE 1
Task and Material-Selective PFC Regions

Brain region	Brodman area	X	Y	Z	Size (mm ³)
Task-selective regions					
WM (two-back)					
Left DL-PFC	46/9	-43	24	27	2106
Right DL-PFC	46/9	37	30	36	918
Right FP-PFC	10	37	48	15	648
Right supplementary motor area	6	25	9	45	783
LTM encoding (intentional)					
Left VL-PFC	45	-52	24	6	270
Right medial FP-PFC	10	17	48	15	756
LTM retrieval (recognition)					
Right frontal operculum ^a	47/Insula	29	12	-3	108
Material-selective regions					
Words					
Left VL-PFC	44/45	-46	12	12	5184
Right VL-PFC	44	61	6	18	432
Faces					
Right VL-PFC	44/45	46	24	15	1944
Right DL-PFC	46/9	40	39	21	243
Right medial FP-PFC	10	20	54	9	243
Right supplementary motor area	6	16	3	66	567

Note. Significant activations are listed for both task-selective and material-selective analyses. Regions are listed according to location of activation centroid. Coordinates are determined from the Talairach and Tournoux (1988) atlas.

^a Region identified in less-stringent analysis (reduced size criteria).

left hemisphere and face-specific regions located in the right hemisphere. Furthermore, the largest regions of activity were located ventrolaterally, with the face and word regions appearing in homologous areas of the inferior frontal gyrus (BA 44/45; see Fig. 2). ROI analyses showed that these VL-PFC regions (and all of the other material-selective PFC regions) showed no difference in activity between memory tasks, as confirmed in an ANOVA by a nonsignificant main effect of task ($F < 1$; see Fig. 2).

DISCUSSION

The results of this study highlight the importance of directly comparing PFC activation in WM and LTM tasks. In particular, we note a number of conclusions that can be drawn from the results. First, bilateral DL-PFC regions were observed to be activated during WM but not during either LTM encoding or retrieval. The identification of DL-PFC activity during WM task performance is not in and of itself a novel result, given that it is among one of the most reliable findings in the cognitive neuroimaging literature (Cabeza and Nyberg, 2000). What is novel is the finding of DL-PFC regions that showed strong differences in activity between WM and LTM tasks. This is an important result given the various reports of PFC activation during LTM tasks, with some suggestion that the same DL-PFC regions active in WM (i.e., BA 46/9) are also activated during at least LTM retrieval (McDermott *et al.*,

1999b; Wagner *et al.*, 1998a). However, no previous study had directly investigated this potential similarity in DL-PFC activity patterns across WM and LTM tasks. Second, no FP-PFC regions were observed to be selectively active during LTM retrieval as compared to WM. Although this is a negative result, it is also noteworthy, given the recent emphasis in the neuroimaging literature on the role of FP-PFC in retrieval (Buckner and Koutstaal, 1998; Lepage *et al.*, 2000; Wagner, 1999). However, our results indicate that, if anything, the *n*-back WM task may more strongly activate FP-PFC regions than LTM retrieval. Consequently, these findings suggests a possible reinterpretation of the functional significance of FP-PFC activity. Third, VL-PFC regions were observed that strongly differentiated between material-types in a lateralized manner, but showed no differences in activity across WM and LTM tasks. This finding suggests that these VL-PFC regions may subservise stimulus-specific but not memory-specific processing functions. This interpretation stands in contrast with other theories suggesting interpretations of these regions that relate specifically to one memory domain, such as that of modality-specific WM buffers (Smith and Jonides, 1997). Finally, we also observed PFC regions that were selectively activated during LTM encoding relative to either LTM retrieval or WM. The finding of encoding-selective activity in PFC was not predicted, and has not been previously highlighted in the literature, but may provide a promising new avenue for future research. Below, we discuss each of

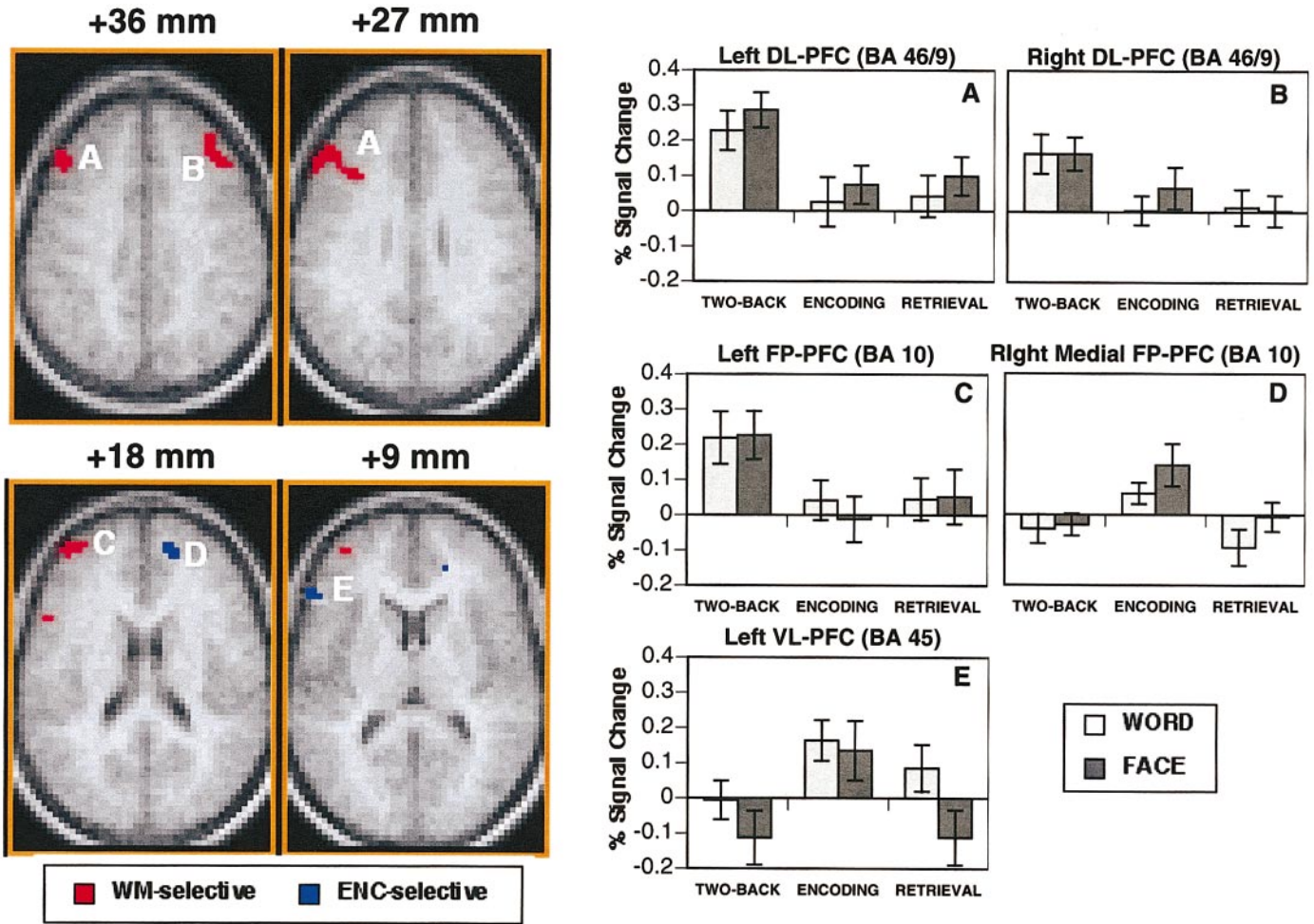


FIG. 1. Task-selective PFC regions. (Left) Activation of WM-selective regions are shown in red and ENC (encoding)-selective regions are shown in blue. Displayed are left (A) and right (B) DL-PFC and left FP-PFC (C), right medial FP-PFC (D), and left VL-PFC (E). Images are in the Talairach and Tournoux (1988) atlas space at various z coordinate locations, with activation overlaid on the corresponding anatomy image. Left of the image refers to the left side of the brain. (Right) Graphs showing percent signal-change (relative to fixation) across the different task and material conditions for these regions. Error bars indicate the standard error of the mean (SEM).

these results in greater detail, focusing on functional interpretations of the findings with regard to different PFC subregions.

DL-PFC

The current results provide support for the hypothesis that DL-PFC regions are preferentially involved with WM functions. A bilateral region of BA 46/9 was found to be significantly activated during WM, but was not engaged by either of the LTM tasks. Moreover, these regions showed no effect of material-type, being equally activated for words and faces. This latter result is consistent with a number of recent neuroimaging studies of WM, indicating that DL-PFC regions typically do not show material-specificity (D'Esposito *et al.*, 1998; Nystrom *et al.*, 2000; Owen, 1997).

There are at least two current models of DL-PFC function that would predict such a pattern. One model,

originally put forth by Petrides and colleagues (Owen *et al.*, 1996; Petrides, 1994), suggests that DL-PFC is specialized for the monitoring and manipulation of items held in WM. This model has been supported by recent event-related neuroimaging studies by D'Esposito and colleagues (D'Esposito *et al.*, 1999; Postle *et al.*, 1999), which show DL-PFC responses specifically associated with manipulation demands during WM task performance. Such a model would account for the current pattern of results, given that the n -back paradigm requires that actively maintained items both be coded for their temporal order (1-back or 2-back) as well as frequently updated with each new stimulus presentation. These monitoring and manipulation processes are not likely to be a component of either LTM encoding or retrieval tasks, since there is no requirement for presented items to be temporally coded or actively updated.

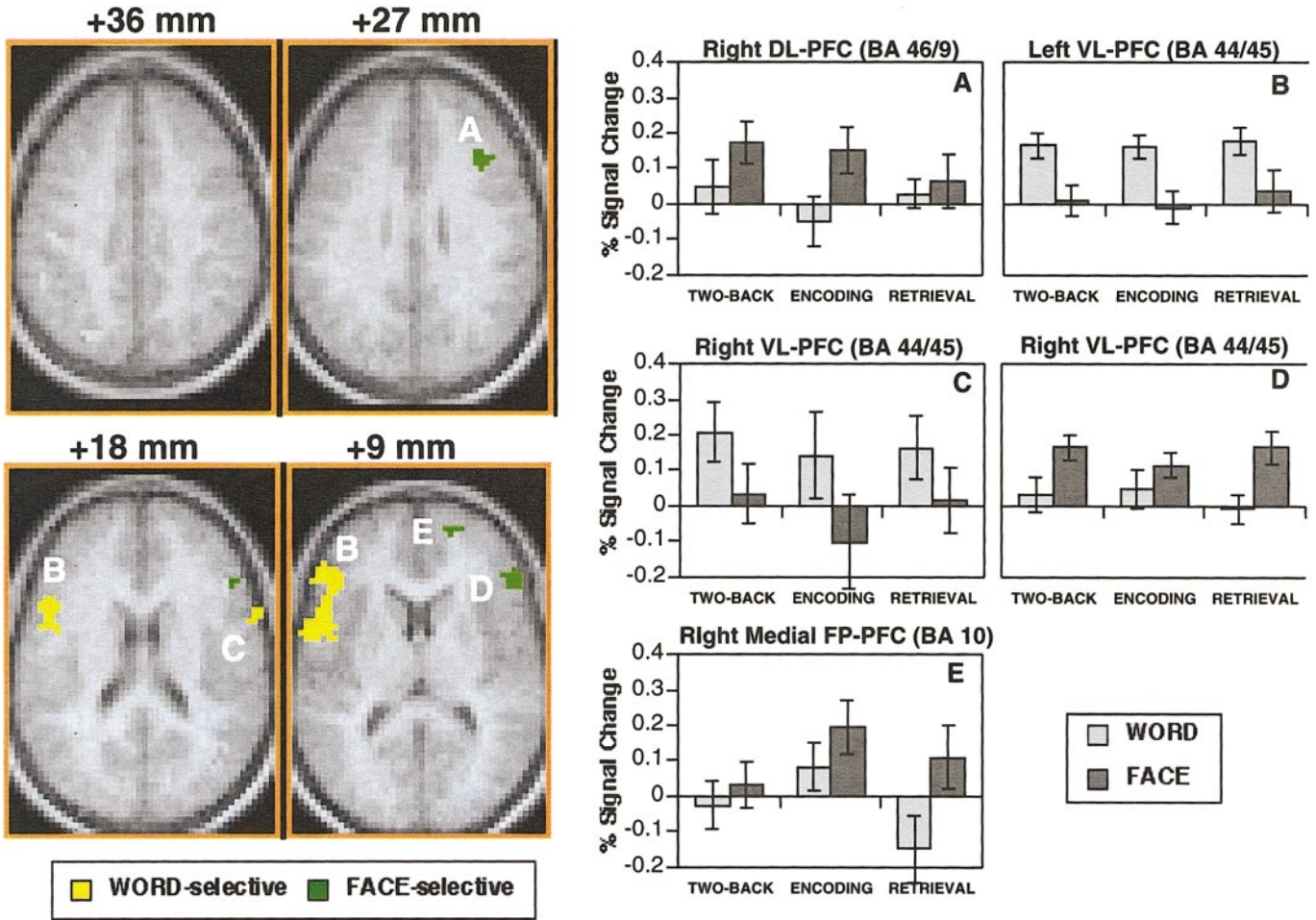


FIG. 2. Material-selective PFC regions. (Left) Activation of word-selective regions are shown in yellow and face-selective regions are shown in green. Displayed are left DL-PFC (A), left (B), right VL-PFC (C, D), and right medial FP-PFC (E). (Right) Graphs showing percentage signal-change (relative to fixation) across the different task and material conditions for these regions.

A second model suggests that DL-PFC is specialized for the active maintenance of context or goal-related information, in order to bias subsequent processing or response selection (Braver and Cohen, in press; Cohen *et al.*, 1996; O'Reilly *et al.*, 1999). This model is supported by event-related imaging studies showing that DL-PFC regions show sustained, load-sensitive activity during the *n*-back task (Cohen *et al.*, 1997), as well as significant delay-related activity during WM tasks specifically requiring active maintenance of context, even with no explicit manipulation demands (Barch *et al.*, 1997, 2001; Braver and Bongiolatti, 2000; Braver and Cohen, in press). Such a model would also account for the current results, given that the *n*-back paradigm requires that information be actively maintained across intervening items in a context-sensitive code that can be used to overcome inappropriate response tendencies (such as the tendency to respond to a 1-back repeat). These functions would not be expected to play a role in either of the LTM tasks, since there is no requirement that items be actively maintained across

trials or that response selection be biased according to prior context. Finally, both the manipulation and context-maintenance models are consistent with the lack of material effects observed in DL-PFC regions. Both models suggest that dorsolateral representations are higher-order ones, and are thus likely to be multimodal in nature.

One potential issue with regard to the current results concerns the role of DL-PFC during LTM retrieval. In particular, a number of studies in the neuroimaging literature have reported the presence of DL-PFC activity during retrieval tasks (Buckner, 1996; Wagner, 1999). Indeed, a recent study has found that right DL-PFC was selectively activated during LTM retrieval as compared to encoding (McDermott *et al.*, 1999b). Although at first blush it may appear as if our results conflict with this finding, in fact they do not. The current results indicate that there are DL-PFC regions which appear to be selectively activated during WM, but they do not indicate whether or not there are other regions of DL-PFC that do show activation dur-

ing LTM retrieval (or encoding). This is because the analysis procedure used in the current study was designed to identify regions showing task or material-selective activity, rather than regions showing activation in multiple tasks (i.e., a conjunction analysis). However, an informal inspection of regions activated during LTM retrieval did indicate the presence of right DL-PFC activity in a location near to the WM-specific region. We did not conduct a formal analysis of this activity because we felt that our use of such a low-level control (fixation) would not permit strong inferences regarding the nature of this activation. Future research will be needed to determine both the extent and functional interpretation of PFC regions commonly activated across WM and LTM domains.

VL-PFC

The results of the current study are consistent with a growing literature indicating the presence of material-specificity within VL-PFC regions. We observed that left hemisphere VL-PFC was selectively engaged during the processing of verbal items (familiar words) whereas right VL-PFC was selectively engaged during processing of nonverbal items (unfamiliar faces). Similar results have been noted in a number of different studies and/or reviews of both the WM (D'Esposito *et al.*, 1998; Smith and Jonides, 1999) and LTM literatures (Kelley *et al.*, 1998; McDermott *et al.*, 1999a; Wagner, 1999). However, as noted above, these two literatures have often been considered in isolation of the other. Thus, interpretations of VL-PFC material-specificity in the LTM literature have been linked to the strength of code-specific encoding processes (Brewer *et al.*, 1998; Kelley *et al.*, 1998; Wagner *et al.*, 1998c). In contrast, in the WM literature, material effects in VL-PFC have been attributed to modality-specific buffers (Smith and Jonides, 1997), in accord with the Baddeley model (Baddeley, 1986). Recent work by McDermott *et al.* (1999a), has questioned the validity of these task-specific interpretations of VL-PFC material effects. In that study, equivalent material effects were observed both during LTM encoding and retrieval. The current results extend those of McDermott *et al.*, by demonstrating that VL-PFC regions not only show the same material effects during different aspects of LTM, but also generalize across memory domains to include WM conditions.

It is possible to interpret the findings of equivalent material-specificity across tasks in a manner that is consistent with a task-specific processing function. For example, one could still argue that the material-specific VL-PFC regions play a special role in LTM encoding. One could argue that the 2-back condition engenders "deep," albeit incidental, encoding of items into LTM because task demands require that items be processed in an elaborative manner (Craik and Lockhart,

1972). Analyses of the recognition performance of subjects support this conclusion, in that recognition accuracy was equivalent for items initially presented during the intentional encoding and two-back conditions. Likewise, LTM retrieval can also serve as a good incidental encoding task. Indeed, a large behavioral literature supports this hypothesis (Glover, 1989), and recent neuroimaging results indicate that, during a retrieval task, VL-PFC activity to new (i.e., distractor) items can be used to predict later recognition of those same items (Buckner *et al.*, in press). It is also possible to argue that VL-PFC activity reflects a privileged role in domain-specific WM processes such as phonological and visuospatial rehearsal (Wagner, 1999). These rehearsal processes might be engaged during LTM encoding in order to facilitate memorization (i.e., maintenance rehearsal) or inter-item association (i.e., elaborative association) and during retrieval to provide a comparison template during memory search.

Although either of these task-specific hypotheses provide plausible explanations of the current results, we prefer a task-independent interpretation of VL-PFC activity on the basis of parsimony. In particular, we would argue that VL-PFC may be engaged during any task that requires extraction of higher-order representational features of items in order to satisfy behavioral goals. The material-specificity of these regions may reflect the fact that extraction of higher-order features often involves capitalizing on the unique properties of verbal and nonverbal items (e.g., phonological/articulatory or semantic information for verbal items, and configural or relational information for nonverbal items). Moreover, once these higher-order features are successfully extracted they would likely facilitate both LTM and WM processes, by helping to uniquely code the identity of each item during both short-term active maintenance and long-term storage and retrieval.

FP-PFC

Contrary to our predictions, we did not observe FP-PFC activation selectively associated with LTM retrieval. In fact, we found evidence of a very different dissociation, with a left hemisphere FP-PFC region showing activation during WM, but not LTM retrieval or encoding. The lack of retrieval-selectivity in FP-PFC was further confirmed by an exploratory analysis which indicated that all of the FP-PFC regions activated by LTM retrieval were equally (or more strongly) activated during WM. Two different interpretations can be made to account for this pattern of results. The first is that performance of the *n*-back WM task often leads subjects to spontaneously adopt an episodic "retrieval mode." Under this hypothesis, rather than actively maintaining items in WM, subjects use the strategy of rapidly encoding each item into LTM, and then use episodic retrieval as a means of making target

determinations for a subsequent presentation. This strategy might be most useful under conditions in which items only repeat when they are targets (i.e., 2-back repeats). However, given that our design of the stimulus sequences for the two-back included a substantial number of nontarget repeated items (including 1-back and 3-back repeats), such a retrieval strategy would be somewhat ineffective. For this reason, it seems less plausible that the retrieval account can adequately explain the results. Nevertheless, it is possible that subjects did use this strategy occasionally, even if it is less effective, as a means of reducing cognitive load (assuming that a retrieval strategy requires less effort than one involving active maintenance).

The second interpretation is that FP-PFC activity may reflect cognitive processes that are not specific to episodic retrieval. Indeed, two previous reviews of FP-PFC activation in functional neuroimaging studies have noted that a number of other tasks have been found to engage this region in addition to episodic retrieval, including complex WM tasks such as the *n*-back (Christoff and Gabrieli, 2000; MacLeod *et al.*, 1998). Moreover, a recent study by Koechlin *et al.* (1999) have suggested that FP-PFC activity may best reflect the requirement for what they term “cognitive branching”—the requirement to actively maintain information related to the primary task goal during the processing of subgoal tasks. Such a hypothesis may account for activation of FP-PFC regions during the *n*-back, in which updating of temporal order information must occur after the presentation of each new stimulus, while at the same time making target determinations based on the previously maintained information. Interestingly, the lack of strong retrieval-related activity in FP-PFC in the current study might be tied to the particular retrieval task used. In a recent review of FP-PFC activation studies, Christoff and Gabrieli (2000) noted that forced-choice recognition was a fairly unreliable elicitor of FP-PFC activity, in comparison with other retrieval tasks, such as free or cued recall. In a hypothesis similar to that of Koechlin *et al.* (1999), Christoff and Gabrieli (2000) suggested that FP-PFC will be most strongly engaged in task situations requiring evaluation of self-generated information. Forced-choice recognition tests permit subjects to evaluate externally provided information (i.e., the test probe), whereas free and cued recall require that subjects self-generate the retrieval cue.

Further research will be needed to better determine which of these two alternative models of FP-PFC function best accounts for the current data. For example, it would be useful to directly manipulate the number of nontarget repeats during the *n*-back task, in order to determine both how this affects subjects' strategy choice and level of FP-PFC activity. Likewise it would be useful to compare WM and LTM retrieval using

cued or free recall instead of forced-choice recognition. This would help to address whether there are in fact retrieval conditions in which FP-PFC is more strongly activated than during WM task performance.

Encoding-Selective PFC Regions

In addition to the WM-selective activity observed in this study, we also found PFC regions which were selectively activated during encoding. However, these findings were not predicted, and so must be treated as somewhat tentative. Nevertheless, a few aspects of these findings are worth commenting upon. The two encoding-specific regions were also found to show material effects that were consistent with the other patterns of material-specificity observed. In particular, we identified a word-specific region in left VL-PFC and a face-selective region in right ventral PFC, although located somewhat medially rather than laterally. Interestingly, the left VL-PFC region was very close to the location of the other material-specific (but not task-specific) region observed in left VL-PFC. However, the nature of our analysis procedure ensured that these two regions were nonoverlapping. Although we did not predict that we would observe this finding, it is consistent with the results of a prior event-related fMRI study (McDermott *et al.*, 1999b), which also observed left BA45 activity to be preferentially engaged during intentional encoding as compared to episodic retrieval of word stimuli. However, interpretations of the significance of both this and the right hemisphere region are difficult to make. One tantalizing possibility is that activation of these regions is somehow reflective of processing strategies specifically associated with intentional, as opposed to incidental encoding. As noted above, the *n*-back and recognition tasks could also be considered incidental encoding tasks, so the intent to memorize items is a primary critical difference between the conditions. Of course, such a hypothesis must be considered highly speculative without further empirical support.

CONCLUSIONS

Our results highlight the importance of examining brain activity across multiple memory domains. By examining the response of PFC and other regions in both WM and LTM tasks within the same subjects, we were able to differentiate regions that were selectively activated by a particular task, such as the DL-PFC, from those that showed selectivity to the material-type of each item, but were equally activated across all tasks (i.e., VL-PFC). We were also able to demonstrate that PFC regions thought to be task-selective (e.g., FP-PFC) actually did not show such a pattern of selectivity. These results support a number of existing hypotheses regarding the functional roles that different

PFC subregions play in memory, and also provide data which may help to constrain the development of new hypotheses.

ACKNOWLEDGMENTS

This work was supported in part by grants from the National Institute of Mental Health (S.E.P.) and McDonnell Center for Higher Brain Function (R.L.B.). The authors thank Marc Raichle for his enthusiastic support, Kathleen McDermott for her thoughtful comments and helpful suggestions, and Sarah Lageman and David Molfese for their technical assistance.

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