

THE major current theory relating brain mechanisms in prefrontal cortex (PFC) to memory for discrete events (episodic memory) emphasizes the role of right PFC during retrieval. Using event-related fMRI, we found both right and left PFC activity during episodic remembering, but only the left PFC activity was related to the amount of episodic detail required at test. We suggest that right PFC subserves relatively simple, heuristic, cognitive processes and that left PFC is recruited for more reflectively demanding, systematic, processes. Episodic remembering often requires such systematic processes and, under those circumstances, recruits left, as well as right, PFC. *NeuroReport* 9: 3509–3514 © 1998 Lippincott Williams & Wilkins.

Key words: Episodic memory; Memory and fMRI; Prefrontal cortex; Recognition; Source monitoring

Left prefrontal activation during episodic remembering: an event-related fMRI study

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Introduction

Research and theorizing about the function of prefrontal cortex (PFC) during episodic memory currently emphasizes the role of the right PFC during episodic memory retrieval. Indeed, as described by the hemispheric encoding/retrieval asymmetry model (HERA),^{1–4} the left PFC is thought to be disproportionately involved in retrieval of semantic information (e.g. the meanings of words), and hence in episodic encoding that accesses semantic information, whereas right PFC is thought to be disproportionately involved in the retrieval of episodic information (memory for specific events, such as the occurrence of a word on a list). Although some researchers have observed left PFC activity during episodic memory tests,^{2,5,6} these activations (when discussed) have typically been thought to be unrelated to the processes involved in episodic remembering. Rather, left PFC activations during episodic remembering have generally been interpreted as reflecting additional encoding (i.e. semantic retrieval) engaged during an episodic memory test as a result of insufficient or shallow encoding of to-be-remembered items during the acquisition task (consistent with the HERA model).

However, a recent review⁷ of neuroimaging studies of episodic memory tests suggests that left PFC may play a more central role in episodic remembering than generally acknowledged. In particular, the pattern of PFC activity across studies suggests that left PFC may support more complex, reflective⁸ processing engaged during more difficult, or detailed, episodic

remembering. In related work, Johnson *et al.*⁹ reported an event-related potential (ERP) study comparing cortical activity during source identification and old/new (O/N) recognition. Source tests, relative to O/N tests, generally involve more specific, detailed identification of the context in which a memory was acquired – that is, more episodic specificity – and are thought to be, on average, more reflectively demanding.^{10,11} Johnson *et al.* identified a frontally distributed difference in cortical activity during source identification and O/N recognition that suggested more left PFC activity during the source than O/N test. Nevertheless, these ERP results do not provide a precise description of the anatomical source for the observed electrophysiological activity. The present event-related fMRI study provides clear evidence for left PFC activity during a source test relative to an O/N test, suggesting that the left (like the right) PFC is functionally associated with episodic remembering.

Materials and Methods

Four healthy, right-handed volunteers (all of whom gave written, informed consent) participated in the study, which was approved by the Institutional Review Boards at Princeton University and the University of Pennsylvania. Brain activity was measured as participants performed each of the two memory tests of interest. Prior to the test scans, participants initially viewed a series of 64 items,¹² half of which were presented as pictures (i.e. simple line drawings) and half of which were presented as words.

Participants performed one of two acquisition tasks with the picture and word stimuli; two participants (ME and ZA) judged the difficulty of drawing each item (judgment was based upon an explicitly formed mental image for word items), and the remaining two participants (EL and PA) rated the number of possible uses they could think of for each item.⁹ (The frontal difference between source and O/N test conditions did not interact with acquisition task in the ERP study; thus both conditions were included here for generality only.) During a subsequent surprise test phase, the 64 old picture and word items were randomly intermixed with 36 new items; all test items were presented as words. For half of the test items (i.e. 16 picture, 16 word, and 18 new), participants performed an O/N test (during experimental fMRI runs 1 and 3), for which they identified each test item as either an old item (i.e. they remembered it as on the acquisition list regardless of whether it was a picture or a word) or a new item (i.e. they did not remember seeing it during the acquisition phase). For the other half of the test items participants performed a source identification test (during experimental fMRI runs 2 and 4), for which they identified each test item as either a word item (i.e. they remembered originally seeing an item as a word), a picture item (i.e. they remembered originally seeing an item as a picture), or a new item. Responses were made by pressing one of two (O/N test) or one of three (source test) buttons. For both the source and O/N tests, trials started with a 500 ms presentation of a cross-hair (indicating the beginning of a trial), followed by a 200 ms presentation of the test item, after which the cross-hair was again presented for 3.8 s. Test trials were separated by an intertrial interval of 11.5 s.

Imaging acquisition: Scanning was carried out on a 1.5 T Signa scanner (GE Medical Systems) equipped with a fast gradient system for echo-planar imaging. A standard radio frequency (RF) head coil was used with foam padding to restrict, comfortably, head motion. High resolution sagittal and axial T1-weighted images were obtained for every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to the blood oxygenation level dependent (BOLD) signal.^{13,14} Resolution was 3.75×3.75 mm in plane, and 5 mm between planes (21 axial slices were acquired). Twenty seconds of gradient and RF pulses preceded the actual data acquisition to allow tissue to reach steady-state magnetization. Each experimental run in the scanner consisted of a block of 25 trials and each subject performed four experimental runs, yielding a total of 100 trials. A total of 200 echoplanar images in time were obtained per slice

in each 400 s experimental run. Thus, a total of 800 observations were obtained for each voxel in the brain for each subject, allowing for a within-subject data analysis.

Image analysis: Off-line data processing was performed on SUN Ultra workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO). After image reconstruction and prior to motion correction, the data were sinc interpolated in time to correct for the fMRI acquisition sequence. This step is of particular importance for our experiment because hemodynamic responses were to be compared across slices that were obtained at different points in the acquisition sequence (and therefore at different points in time). If left uncorrected, this would have introduced considerable variability and bias (a phase advance) into the hemodynamic responses. The data were then motion corrected. First, a six parameter, rigid-body, least squares realignment routine was used¹⁵ without correction for spin history.¹⁶ Next, a slice-wise motion compensation method was utilized that removed spatial coherent signal changes via the application of a partial correlation method to each slice in time.^{17,18} Voxel-wise analysis of the functional imaging data was conducted to identify voxels with a significant response to the episodic remembering events. Because fMRI data are temporally autocorrelated under the null hypothesis,^{17,18} statistical maps were created within the framework of the modified general linear model of Worsley and Friston¹⁹ using a basis set of shifted impulses.²⁰ Each sixteen second trial resulted in eight data points. Five shifted impulse covariates were included, each of which modeled one of the second through sixth (inclusive) time points of all trials. The other time points (first, seventh and eighth) were left as unmodeled, baseline points. Activated voxels were identified for each subject for the main effect of the behavioral task by using the summed effect of the third and fourth independent variables (corresponding to 6 s and 8 s following the onset of the target stimulus). Each statistical map was then thresholded at a critical t-value of 4.5 corresponding to a Bonferroni corrected, map-wise $\alpha = 0.05$. Prefrontal regions identified in this manner were then tested for differences between conditions of the behavioral task. Within the matrix of the GLM¹⁹ was placed a time-domain representation of the expected $1/f$ power structure¹⁸ along with a filter designed to remove low frequency confounds (< 0.025 Hz) and high frequency noise at and around the Nyquist frequency (0.25 Hz). It should be noted that these filtering components have no effect upon the shape of the responses obtained, as they affect frequencies that are either below that of the task or

above that passed by the hemodynamic response of the system. For display purposes these thresholded maps and the T1 anatomical images were transformed to Talairach space²¹ by a 12 parameter affine transformation,¹⁵ with non-linear deformations.²²

Results

The mean response time during the source test (1831 ms) was significantly longer ($t(3) = 3.65$, $p = 0.035$) than during the O/N test (1251 ms). As measured by corrected recognition (i.e. hits-false alarms), the ability to discriminate between old and new items did not differ depending upon whether participants were engaged in the source test (mean = 0.77) or the O/N test (mean = 0.75). The mean source identification performance (i.e. the proportion of items correctly identified as old that were also correctly identified as either pictures or words) was 0.68 during the source test.

Looking first at the left PFC, significant activity, relative to the intertrial interval, was observed during episodic remembering (i.e. the source and O/N tests combined) in all four participants (see Table 1). The extent of the left PFC activation included Brodmann areas 46, 44, 10, and 9, consistent with other neuroimaging studies of episodic memory retrieval that have reported left PFC activity.^{5,6,23-28} Subsequent contrasts of the source and O/N tests were conducted by comparing (with t -tests Bonferroni corrected for multiple comparisons) mean signal associated with each test condition within each region of activity identified in Table 1. For three of the four participants (ME, PA, and ZA) the magnitude of activation for the source and O/N tests in one or more of these activated left PFC regions was significantly different (see Table 1). These differences reflected increased

BOLD signal during the source test relative to the O/N test (evidenced by the positive t -values in Table 1). The full extent of left PFC activation present for both remembering tasks in which the source and O/N test differed (in all cases source > O/N) can be seen in Fig. 1. The time-course of the event-related BOLD signal can be seen in Fig. 2, which plots the mean signal across trials for the source and O/N tests at each scan point (every 2 s) following the presentation of a test stimulus.

A similar pattern of activity was also observed for the fourth participant (i.e. for EL, the magnitude of left PFC activity was greater for source identification than for old/new recognition), although this difference failed to reach significance. Interestingly, the response time difference between the source and O/N tests for EL (336 ms) was also less than the group mean (581 ms), which in combination with the pattern of EL's activations across the two tests suggests the possibility that the strategies adopted by this participant for the two test tasks were more similar than those adopted by other participants. As can be seen, the within-subject analysis procedure used here allows one to statistically control error rates for each participant while observing patterns of variability/consistency across participants (analogous to analysis techniques used, for example, in small n , electrophysiological studies of non-human primates). This allows maximal preservation of information regarding structure-function relationships. Nonetheless, an analysis of the left PFC activity including all four participants revealed that the mean difference observed between the source and O/N tests (calculated as an average for each participant of the t -values presented in Table 1) was significantly greater than 0 (i.e. the mean t -value expected given that there was no difference between the two tests), with $t(3) = 4.41$, $p < 0.03$.

Table 1. Left PFC activations associated with episodic remembering and the t -statistic for the subsequent comparison of source identification and old/new recognition within each region.

Participant	Talairach coordinates			BA	Source > O/N ^a
	x	y	z		
EL	-56	45	0	10/44	0.61
	-60	23	25	46	0.89
	-45	41	30	9/46	0.81
ME	-56	38	30	10/46	2.95*
	-60	11	35	9	2.05*
PA	-56	41	0	10/47/44	1.99*
	-60	26	10	46/45	2.41*
ZA	-45	56	15	10	0.86
	-60	15	30	9/44	1.97*

^aPositive t -values reflect greater signal for source relative to O/N test, and negative t -values reflect greater signal for O/N relative to source test.
 $p < 0.05$, Bonferroni corrected for number of individual activations in which the source and O/N tests were compared.

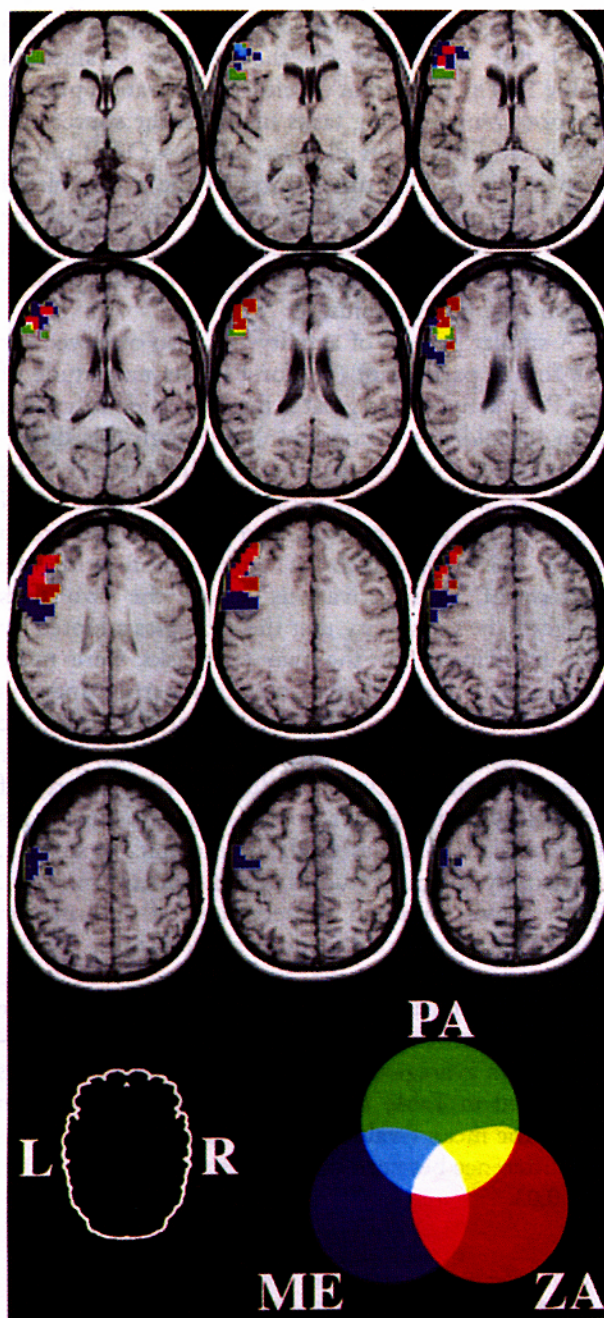


FIG. 1. Threshold map of left PFC regions activated by both the source identification (source) and old/new (O/N) recognition tests combined (relative to the intertrial interval) in which the magnitude of the mean BOLD signal during the source and O/N tests were significantly different (Bonferroni corrected for the number of individual activations in which the source and O/N tests were compared). In all cases these differences reflected greater activation during the source than during the O/N test. Three participants are shown ME (Blue) PA (Green) and ZA (Red); intermediate colors indicate common areas where the BOLD signal during the source test was significantly greater than O/N in two or more participants.

Mean BOLD Signal

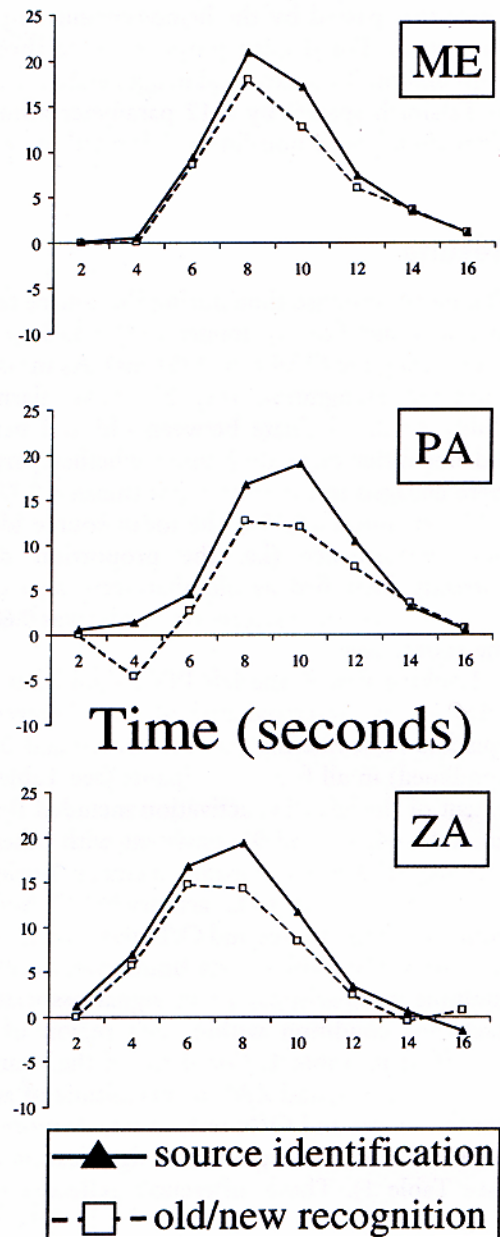


FIG. 2. Mean left PFC BOLD signal for source identification (source) and old/new (O/N) recognition test trials observed throughout the 16 s trial epoch following the onset of a test stimulus. Reported separately for those individuals for whom the mean BOLD signal was significantly greater during the source test than during the O/N test (in regions of left PFC active during source and O/N tests combined); a single significant activation cluster is represented for ZA and data are averaged across 2 significant activation clusters each for ME and PA.

Table 2. Right PFC activations associated with episodic remembering and the t-statistic for the subsequent comparison of source identification and old/new recognition within each region.

Participant	Talairach coordinates			BA	Source > O/N ^a
	x	y	z		
EL	34	23	10	45/44	-1.43
	53	8	35	9	1.02
ME	49	15	0	47	0.50
	41	45	10	10/46	1.94
	53	26	30	9/46	1.23
	45	0	40	9/46	1.54
PA	23	45	40	8	-0.34
	41	49	-5	10	-0.05
	34	23	5	45	-0.88
	49	19	20	45/46	-0.07
	34	49	30	9/46	-0.14
	49	0	30	44	1.00
ZA	38	49	25	10/9	-1.31
	19	45	30	9	0.68
	41	30	40	8/9	-0.29
	26	38	50	8	0.67

^aPositive t-values reflect greater signal for source relative to O/N test, and negative t-values reflect greater signal for O/N relative to source test.
 $p < 0.05$, Bonferroni corrected for number of individual activations in which the source and O/N tests were compared.

In the right PFC, significant clusters of activation associated with episodic remembering were also observed (see Table 2). The extent of activation in right PFC included Brodmann areas 46, 45, 44, 10, 9, and 8, consistent with activity previously described across a variety of conditions.^{3,5,6,29-31} However, in contrast to the left PFC, comparisons of the BOLD signal associated with the source and O/N tests within each activated region of right PFC failed to produce any significant differences for any of the participants (see Table 2). For eight of the activations, the magnitude of activity was greater for the source than for the O/N test, whereas for the remaining eight activations, the magnitude of activity was greater for the O/N than the source test (as evidenced by negative t-values), and the mean difference observed between the source and O/N tests (calculated as an average of the t-values presented in Table 2) was not significantly different from zero ($t(3) = 0.42$, $p > 0.70$). This outcome suggests that right PFC activity did not increase in this study with task demands requiring increasing episodic specificity. Thus, unlike the left PFC, no consistent difference in activity between the two test conditions was evident in the right PFC.

Discussion

What is the possible functional significance of the left PFC activity observed in this study? As already noted, a number of researchers have proposed that activation of the left PFC during episodic remembering reflects encoding (semantic retrieval)

engaged for items initially learned under conditions of relatively minimal encoding (e.g. acquisition tasks involving shallow processing).^{2,5,6} However, this explanation fails to account for the pattern of results observed in the present study. Participants in our study performed identical acquisition tasks for the source and O/N test items. Consequently, a more likely hypothesis is that the greater left PFC activity observed in the source test in this study was related to the greater specificity in the episodic information required to perform the source than the O/N test. This outcome would not be predicted by the HERA model, which posits that episodic retrieval is particularly dependent upon right PFC and thus differences in cortical activity as a result of the episodic detail required by memory tasks should be present primarily in the right, rather than the left, PFC.

Alternatively, Johnson and colleagues^{7,10,32} suggest that processes supported by the left and right PFC may be differentially engaged as a function of the reflective demands of a task. According to this idea, regions in the right PFC primarily support more heuristic processes: relatively simple, quick processes sufficient for less reflectively demanding tasks (e.g. memory judgements based on familiarity). Regions in the left PFC primarily support more systematic processes. Systematic processes (and the region of cortex subserving them) are likely to be engaged as the reflective demands of a task increase, such as when retrieval of additional information or more detailed evaluations of activated information are required during episodic remembering. Burgess and Shallice³³ have also suggested that right and left PFC

may be differentially involved in different aspects of episodic remembering.

Both source and O/N tasks engage some combination of relatively simple, heuristic processes and more complex, systematic processes to attribute a context to particular memories. However, because source tasks typically require more deliberative, detailed retrieval and analysis of information (e.g. as when determining whether test items were originally seen as pictures or words), they are on average more reflectively demanding (as evidenced by the greater response time during the source test) than are O/N tasks.¹⁰ With respect to the specific memory tests used in this study, then, identifying whether an item was originally presented as a picture or word (source test) required more episodic information than identifying an item as previously presented (O/N test). Participants would have been more likely to engage more complex reflective processing during the source test than during the O/N test, accounting for the greater activity in left PFC. This explanation is consistent with findings of increased left PFC activity with increasing reflective demands from neuroimaging studies of problem solving³⁴ and semantic judgement³⁵ tasks. This suggests that the processing differences between left and right PFC identified by the present results are not specific to episodic memory but rather reflect a cognitive processing architecture^{36,37} that will be manifested across a range of cognitive tasks.

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