Published in final edited form as:

Neuropsychologia. 2009 October ; 47(12): 2409–2416. doi:10.1016/j.neuropsychologia.2009.04.010.

Right dorsolateral prefrontal cortex is engaged during post-retrieval processing of both episodic and semantic information

Hiroki R. Hayama and Michael D. Rugg

Center for the Neurobiology of Learning and Memory, and Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA 92697-3800

Abstract

Post-retrieval processes are engaged when the outcome of a retrieval attempt must be monitored or evaluated. Functional neuroimaging studies have implicated right dorsolateral prefrontal cortex (DLPFC) as playing a role in post-retrieval processing. The present study used fMRI to investigate whether retrieval-related neural activity in DLPFC is associated specifically with monitoring the episodic content of a retrieval attempt. During study, subjects were cued to make one of two semantic judgments on serially presented pictures. One study phase was followed by a source memory task, in which subjects responded ‘new’ to unstudied pictures, and signaled the semantic judgment made on each studied picture. A separate study phase was followed by a task in which the studied items were subjected to a judgment about their semantic attributes. Both tasks required that retrieved information be evaluated prior to response selection, but only the source memory task required evaluation of retrieved episodic information. In both tasks, activity in a common region of right DLPFC was greater for studied than for unstudied items, and the magnitude of this effect did not differ between the tasks. Together with the results of a parallel event-related potential study (H.R. Hayama et al., *Neuropsychologia* (2008), 46, 1211–1223), the present findings indicate that putative right DLPFC correlates of post-retrieval processing are not associated exclusively with monitoring or evaluating episodic content. Rather, the effects likely reflect processing associated with monitoring or decision-making in multiple cognitive domains.

Keywords

DLPFC; episodic memory; fMRI; monitoring; recollection; source memory

Numerous functional neuroimaging studies of recognition memory have reported greater activity in prefrontal cortex (PFC) for items correctly recognized as studied (old) relative to items correctly rejected as new (for review see: Fletcher & Henson, 2001). Here, we focus on a region of right dorsolateral prefrontal cortex (DLPFC) which is among the PFC regions that demonstrate such old/new differences and which, it has been suggested, supports ‘post-retrieval’ processes (Henson, Rugg, Shallice, Josephs, & Dolan, 1999a; Rugg, Otten, & Henson, 2002; Rugg, 2005) – processes engaged when there is a need to monitor and/or evaluate the products of a retrieval attempt in light of current behavioral goals. It has been argued that post-retrieval processing, as manifest by right DLPFC activity, is engaged either

Correspondence: Hiroki R. Hayama, Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, CA 92697-3800. Email: E-mail: hhayama@uci.edu. Telephone: 949-824-8861. Fax: 949-824-4807.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

when the products of an episodic retrieval attempt must be monitored and evaluated to select a response, as in tests of source memory (Henson, Shallice, & Dolan, 1999b; Rugg, Henson, & Robb, 2003), or when the information retrieved is impoverished, leading to uncertainty as to whether retrieval has been successful (Henson et al., 1999a; Henson, Rugg, Shallice, Dolan, 2000).

An alternative proposal concerning the role of the right DLPFC in memory retrieval posits that this region is activated not by the demands of post-retrieval processing, but rather in proportion to the number of internal decisions required prior to response selection (Dobbins & Han, 2006). In support of this proposal, Dobbins & Han (2006) demonstrated that engagement of right DLPFC was greater for identically formatted recognition memory test items presented in the context of a 'same-different' (are both items old or new?) compared to a 'forced-choice' (which item is old?) task. This prompted the investigators to conclude that right DLPFC was sensitive not to monitoring demands, but rather to the number of internal decisions required by a task (two decisions are required for the same-different judgment whereas only one decision is needed for forced choice). Furthermore, both Dobbins & Han (2006) and Fleck et al., (2006) have demonstrated that the engagement of right DLPFC is not specific to the requirement to monitor or evaluate episodic information. In both studies, right DLPFC activation was evident when judgments were made about stimulus attributes that were available online as well as when the relevant information had to be retrieved from memory. Together, these findings suggest that activation of the right DLPFC during episodic retrieval reflects engagement of cognitive operations that play a wider role than just the monitoring of the outcome of an episodic retrieval attempt.

Turning to event-related potential (ERP) studies of recognition memory, it has been consistently reported that ERP waveforms elicited by correctly identified old items are more positive-going than waveforms elicited by items correctly rejected as new. On the basis of a combination of functional, temporal, and topographic criteria, these ERP 'old/new effects' have been dissociated into a number of functionally and neurally distinct modulations. Of particular interest in the present context is the 'right frontal' old/new effect, which takes the form of a relatively late-onsetting, sustained modulation that, as its name implies, is maximal over the right frontal scalp. Analogous to the engagement of right DLPFC in fMRI studies, the right frontal effect is elicited by studied items requiring source judgments (Senkfor & Van Petten, 1998; Wilding & Rugg, 1996), as well as by recognition test items when there is uncertainty about their study status (Rugg, Allan, & Birch, 2000; Ullsperger, Mecklinger, & Müller, 2000). On the basis of these functional parallels, it has been proposed that first, the right frontal effect reflects engagement of post-retrieval processing, and second, that the right frontal effect reflects, at least in part, activity in right DLPFC (Wilding & Rugg, 1996; Friedman & Johnson, 2000; Rugg et al., 2002; Rugg 2005).

To the extent that the foregoing proposal is valid, it should be possible to demonstrate that, like engagement of right DLPFC, the right frontal ERP effect can be elicited in conditions that do not require the monitoring of the products of an episodic retrieval attempt. Hayama et al. (2008) tested this prediction in two experiments. In the first experiment, subjects were required to respond discriminatively to test items that were judged to be old on the basis of the items' study context in one condition (a source memory judgment), and on the basis of whether they possessed a particular semantic attribute in a second condition (a non-episodic judgment). Virtually indistinguishable right frontal effects were elicited by old items in each condition, suggesting that the effect is not specifically associated with monitoring the products of an episodic retrieval attempt. In the second experiment, subjects made on-line semantic judgments about old items in one test condition, and about new items in the other condition. The right frontal effect was elicited by whichever class of item (old or new) requiring the semantic judgment. Together, these findings appear more consistent with a decisional than a monitoring

account of the right frontal ERP effect and, by extension, of the role of the right DLPFC in retrieval processing (cf. Dobbins & Han; 2006).

In the present study, we acquired fMRI data in an experimental paradigm almost identical to that adopted in the first experiment of our previous study (Hayama et al., 2008). During study, subjects were cued to make one of two semantic judgments on serially presented pictures. Memory for the pictures was later tested in two separate test tasks. In the 'source' task, subjects responded 'new' to pictures judged to be unstudied, and, for each picture judged to be studied, responded differentially depending upon the semantic judgment that had been made at study. In the 'semantic' task, subjects again responded 'new' to unstudied pictures, whereas studied items required, not a source memory judgment, but a judgment about a semantic attribute that had not been evaluated at study. Importantly, whereas successful performance on both tasks necessitated the retrieval from memory of information sufficient to support the initial (covert) old/new decision, only the source task required evaluation of the content of the retrieved information. By contrast, successful performance on the semantic task depended on the evaluation of 'on-line' semantic information rather than retrieved episodic information.

The neural correlates of successful retrieval were operationalized by identifying regions where activity was greater for correctly classified old items compared to correctly rejected new items ('old>new' effects). If the right DLPFC is engaged specifically by the requirement to monitor and evaluate retrieved episodic information, old>new effects in this region should be greater (or perhaps, only evident) in the source task than the semantic task. By contrast, if retrieval-related DLPFC activity is not specifically associated with the monitoring of episodic information, or if it reflects the number of internal decisions preceding a behavioral response (Dobbins & Han, 2006), right DLPFC old>new effects should be equally evident in both tasks. On the basis of our prior ERP study (Hayama et al., 2008), we expected that the findings would conform to the second of these two scenarios.

Materials and Methods

Subjects

Eighteen volunteers from the UCI consented to participate in the study. All volunteers reported themselves to be in good general health, right-handed, with no history of neurological disease or other contra-indications for MR imaging, and to have learned English as their first language. Volunteers self-reported no history of color-blindness, and were tested for color discrimination prior to participating in the experiment. Volunteers were recruited from the University of California at Irvine (UCI) community and remunerated for their participation, in accordance with the human subjects procedures approved by the Institutional Review Board of UCI. The data from 2 subjects were excluded from all analyses: 1 subject for having fewer than 12 trials in two of the critical experimental conditions, and 1 subject for failing to follow instructions. Data are reported from the remaining 16 subjects (12 males) ranging in age from 18 to 30 (mean = 21).

Stimuli

A pool of 192 nameable color pictures of individual objects served as the experimental stimuli. One hundred and sixty pictures were used as the critical study and test items, twenty were used in a practice phase preceding the experiment proper, and the remaining twelve were used as study buffers (2 at the beginning and end of each study list), and test buffers (2 at the beginning of the test list). The critical stimuli were selected such that equal numbers of items could be categorized according to each of three semantic judgments: animacy (living or not-living), size (bigger or smaller than a shoebox), and location (more likely to be found indoors or outdoors). For each of the 8 possible combinations of these categories (i.e. living, small, indoor; non-

living, small, indoor; and so forth), there were 20 items. For each subject, the 160 critical pictures were randomly assigned to 4 groups of 40 items, with the restriction that each group contained 5 items from each of the 8 categorical combinations. The items from two of these groups were presented in separate 40-item study phases and subsequently served as old pictures during the corresponding test phases. The items from the remaining groups served as new items in the two 80-item test phases.

Procedure

Each study trial consisted of the presentation of a red fixation character (+) presented at the center of the gray frame for 1200 ms, a semantic judgment cue for 1200 ms, a picture for 1000 ms, and a centrally-presented black fixation character (+) for 2400 ms. Each test trial consisted of a red fixation for 500 ms, a test picture for 1000 ms, and a centrally-presented black fixation character for 3000 ms. The stimuli were back-projected onto a screen and viewed via a mirror mounted on a sensitivity encoding (SENSE) headcoil subtending a maximum of 5.7° vertical and horizontal visual angles.

Instructions and practice were administered prior to entering the fMRI scanner. For the study phases, subjects were informed that they would see one of two words and then a picture immediately afterwards. The word signified the type of judgment to be made on the picture that followed (BIG?, LIVING?, or INDOOR?). For each subject, two of the semantic judgments (size, animacy, or indoor/outdoor) were used during the study phases, and the remaining judgment was used for the semantic test phase. For one of the study judgments, subjects were instructed to use the index and middle finger on the designated hand to signify a yes or no response, respectively, to the judgment (e.g. index - bigger than a shoebox, middle - smaller than a shoebox). For the other judgment, the respective fingers on the other hand were used (e.g. index - indoors, middle - outdoors).

One of two types of retrieval task (source or semantic) followed each study phase. In both retrieval tasks, a series of pictures were presented, and subjects were instructed to respond 'new' with the index finger of the designated hand to unstudied pictures. In the source task, subjects were instructed that if a test item was 'old', they should signal the semantic judgment made on the picture at study, using the index or middle finger of the hand not employed for new responses. In the semantic task, the requirement was to make a semantic judgment on each old item, again using the index or middle finger of the hand not employed for new responses. Crucially, the semantic dimension on which the item was judged differed from either of those employed during the study phase. The three semantic dimensions (i.e., size, animacy, indoor/outdoor) were rotated across subjects so that they were employed equally often in the study and the semantic test phases. Mapping of responses to hands and the order of administration of the different test tasks, were counterbalanced across subjects. For both study and test tasks, speed and accuracy of responding were given equal emphasis in the instructions.

fMRI Data Acquisition

A Philips Achieva 3T MR scanner (Philips Medical Systems, Andover, MA, USA) was used to acquire both T_1 -weighted anatomical volume images (256×204 matrix, 1mm^3 voxels, 150 slices, axial acquisition, 3D MP-RAGE sequence) and T_2^* -weighted echoplanar images (EPI) [80×80 matrix, 3mm^3 voxels, transverse acquisition, flip angle 70° , echo time (TE) 30ms] with blood-oxygenation level dependent (BOLD) contrast, SENSE reduction factor of 2 on an eight-channel parallel imaging head coil. Each EPI volume comprised thirty 3mm-thick axial slices separated by 1mm, oriented parallel to the AC-PC line, and was positioned to give full coverage of the cerebrum and most of the cerebellum. Data were acquired in two sessions comprised of 290 volumes each, with a repetition time (TR) of 2 seconds per volume. Volumes

within sessions were acquired continuously in ascending sequential order. The first five volumes of each session were discarded to allow equilibration of tissue magnetization.

fMRI Data Analysis

Statistical Parametric Mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK: <http://www.fil.ion.ucl.ac.uk/spm5.html>; Friston et al., 1995) implemented under Matlab2006a (The Mathworks Inc., USA) was used for fMRI data analysis. Functional images were subjected to a two-pass spatial realignment. Images were realigned to the first image, generating a mean image of the sessions. In the second pass the raw images were realigned to the generated mean image. The images were then subjected to reorientation, spatial normalization to a standard EPI template (based on the Montreal Neurological Institute (MNI) reference brain; Cocosco et al., 1997) and were smoothed with an 8mm FWHM Gaussian kernel. For each voxel, the image time-series was highpass-filtered to 1/128 Hz and scaled within-session to yield a grand mean of 100 across voxels and scans.

Statistical analysis was performed in two stages of a mixed effects model. In the first stage, the neural activity was modeled by a delta function (impulse event) at stimulus onset. The ensuing BOLD response was modeled by convolving the neural functions with two hemodynamic response functions (HRFs). The first, hereafter the 'early' HRF, was modeled by a canonical HRF (Friston et al., 1998). The second, - the 'late' HRF - was modeled by a canonical HRF shifted one TR (2 seconds) later in time, and was included to capture any delayed responses. Importantly, the covariates for the late HRF were orthogonalized with respect to the covariates for the early HRF using the Gram-Schmidt procedure such that any shared variance was attributed to the early HRF (Andrade et al., 1999). An AR(1) model was used to estimate and correct for non-sphericity of the error covariance (Friston et al., 2002). The resulting GLM was used to obtain parameter estimates representing the activity elicited by the events of interest.

For the source task, three event types were defined, consisting of correct source responses to old items, correct rejections to new items, and events of no interest (buffer trials and trials with incorrect or omitted responses). For the semantic task, three analogous event types were defined: correct semantic attributions to old items, correct rejections of new items, and events of no interest. Also included for each session were six covariates to capture residual movement-related artifacts (three rigid-body translation, and three for rotation) along with session-specific constant terms modeling the mean over scans.

The linear contrasts of the parameter estimates for each subject comprised the data for the second stage analyses, which treated subjects as a random effect. Unless otherwise noted, only effects surviving an uncorrected threshold of $p < 0.001$ with nine or more contiguous voxels are reported. The peak voxels of clusters exhibiting reliable effects are reported in MNI coordinates. Exclusive masking was used to identify voxels where effects were not shared between two contrasts. Contrasts to be masked were thresholded at $p < 0.001$ and the SPM constituting the exclusive mask was thresholded at $p < 0.1$ (note that the more liberal the threshold of an exclusive mask, the more conservative is the masking procedure). Time-courses of item-related responses were estimated with a Finite Impulse Response (FIR) model applied to all voxels within a 5mm radius sphere centered on the voxel exhibiting the peak effect (Brett et al., 2002).

Results

In what follows, 'correct old' judgments refer to correct source or correct semantic judgments on studied items. 'Incorrect old' judgments refer to incorrect source or semantic judgments on

studied items. All analyses utilized data associated with correct old responses and correct rejections (correct classifications of new items), unless otherwise specified.

Behavioral Performance

Mean proportions and response times (RTs) for correct old judgments, incorrect old judgments, and correct rejections are listed in Table 1. To test whether item memory differed according to task, response categories were collapsed over correct old and incorrect old judgments to form 'collapsed old' categories for the source and semantic tasks (proportions of old items identified as old were 0.88 and 0.91 respectively). ANOVA [with factors of task (source vs. semantic) and item type (collapsed old vs. new)] gave rise to a main effect of item type [$F(1,15) = 10.25, p < 0.01$], reflecting more accurate performance for new items. There were no significant differences in recognition performance as a function of task.

ANOVA restricted to correct responses [factors of task and item type (old vs. new)] gave rise to main effects of task and item type [$F(1,15) = 8.09, p < 0.05$ and $F(1,15) = 49.99, p < 0.001$, respectively] as well as a task $\times$ item type interaction [$F(1,15) = 8.45, p < 0.05$]. Subsidiary ANOVAs conducted separately on the data for each item type indicated that old items were more likely to be classified correctly in the semantic task than the source task [$F(1,15) = 8.93, p < 0.01$], whereas accuracy for new items did not differ across the tests ($F < 1$).

ANOVA of RTs for correct responses gave rise to a main effect of item type [$F(1,15) = 166.81, p < 0.001$], and a task $\times$ item type interaction [$F(1,15) = 32.28, p < 0.001$]. Subsidiary pairwise contrasts revealed that old items were responded to more slowly than new items in both tasks [$F(1,15) = 220.44, p < 0.001$ and $F(1,15) = 66.9, p < 0.001$, for the source and semantic tasks respectively]. In addition, RTs to new items were shorter in the source task than the semantic task [$F(1,15) = 6.55, p < 0.05$], whereas RTs to old items were longer in the source task [$F(1,15) = 19.27, p < 0.005$].

fMRI Findings

Analysis of the fMRI data was first directed at identifying regions where activity was greater for correct old judgments than for correct rejections regardless of the nature of the retrieval test (main effect of old>new), and vice versa (main effect of new>old). A second analysis focused on regions demonstrating old/new by task interactions.

Common old>new effects

Effects common to the two tasks were identified by exclusively masking each single-sided main effect (old>new, and new>old; each thresholded at $p < .001$) by the outcome of the (two-sided) F-contrast of the old>new $\times$ retrieval task interaction (thresholded at $p < .1$). Thus, voxels where old/new effects differed as a function of task ($p < .05$ one-sided) were removed.

Regions exhibiting old>new effects common to the two tasks are detailed in Table 2 and illustrated for selected regions in Figures 1 and 2. For the early HRF, common effects were identified in bilateral prefrontal and parietal cortex (more extensively on the left), and in left inferior temporal cortex. Analysis with the late HRF identified regions in left inferior temporal cortex, bilateral ventrolateral prefrontal cortex (VLPFC), right medial occipital cortex, and crucially, right DLPFC.

Whereas old/new effects common to the two tasks were identified in right DLPFC with the late HRF, no region of right DLPFC was identified at the pre-experimental statistical threshold in the analysis employing the early HRF. Extracted time courses for a 5mm radius surrounding the peak activity in right DLPFC (Figure 2) suggests that the effects onset sufficiently early to be detectable with the early HRF. Therefore parameter estimates for both the early and late

HRFs were extracted from the right DLPFC peak voxel identified by analysis of the late HRF. ANOVA conducted on these estimates (factors of HRF (early vs. late), item type (old vs. new), and task) revealed a significant old/new effect [$F(1,15) = 11.57, p < 0.005$] that was unmodified by HRF or task. A separate ANOVA on the parameter estimates derived from the early HRF revealed a main old/new effect [$F(1,15) = 4.91, p < 0.05$], again unmodified by task. Thus, these findings demonstrate the presence of a temporally sustained, task-invariant right DLPFC old/new effect.

Common new>old effects

As detailed in Table 3 and illustrated for selected regions in Figure 3, analysis with the early HRF identified widespread new>old effects common to the two tasks. Effects loading on the early HRF were found bilaterally within the anterior extent of the medial temporal lobe (MTL) with local peaks corresponding to left and right hippocampus. A further effect was identified in the right hippocampus with the late HRF. As is also evident from Table 3 and Figure 3, new/old effects were identified in several other regions, including a large expanse of medial PFC.

Old>new × task interaction

Results of the analysis with the early HRF are detailed in Table 4. Greater old>new effects for the source compared to the semantic task were identified in left anterior and medial superior prefrontal cortex, left lateral parietal cortex, and left precuneus. Follow up analyses were performed by inclusively masking the simple old>new effect for each task (thresholded at $p < 0.05$) with the task × old/new interaction ($p < 0.001$). These masks revealed significant old>new effects in the source task in all four regions. Left lateral parietal cortex and left precuneus also demonstrated significant old>new effects in the semantic task. No clusters were identified where old>new effects were greater for the semantic task than the source task, nor were any effects revealed by the interaction contrasts for the late HRF.

Discussion

Behavioral Results

For both tasks, RTs were longer and accuracy was lower for correct old items compared to correct new items. The substantial RT differences between old and new items suggest that subjects first determined whether an item was old or new, initiating a source or semantic judgment only for words judged old. This strategy is akin to what Kahn et al. (2004), have termed ‘familiarity-gated recollection’ and was evident in our prior ERP study (Hayama et al., 2008) as well as other source memory tasks (e.g. Rugg et al., 2003; Van Petten, Senkfor & Newberg, 2000). It is noteworthy, however, that although correct rejection rates were equivalent across the tasks, RTs to new items were significantly faster in the source than the semantic task. Evidently, the initial old/new decision and the subsequent task-specific judgment were not as independent as is implied by the above account. One possibility is that the demands of the source task, with its greater dependence on retrieved information, encouraged more efficient processing of the test items (that is, a more efficient ‘retrieval orientation’; Rugg and Wilding, 2000).

For correct old items, RTs were slower and accuracy was lower in the source task than the semantic task. Whereas these performance differences potentially complicate interpretation of task-wise differences in BOLD effects, they do not compromise interpretation of effects common to the two tasks. It is these common effects that are the focus of the discussion below.

fMRI Findings

Old > New effects—The primary aim of the current experiment was to determine whether retrieval-related activity in right DLPFC is selectively associated with the requirement to monitor the products of episodic retrieval. To address this question, we employed two test tasks that differed with respect to the type of information (episodic vs. semantic) requiring post-retrieval evaluation. Activity in right DLPFC was enhanced by a similar extent for old relative to new items in the two tasks. Thus, right DLPFC was not selectively engaged by the requirement to monitor or evaluate the products of an episodic retrieval attempt.

The present findings can be accommodated within the framework proposed by Dobbins & Han (2006). These authors reported that right DLPFC activity co-varied with the number of internal decisions preceding a behavioral response, regardless of whether or not the decisions were based upon evaluation of retrieved episodic information (see Introduction). In the present study, although all test items required a judgment about their study status, only items identified as old required an additional judgment. Thus, right DLPFC was engaged to a greater extent by test items requiring two judgments as opposed to a single judgment, consistent with Dobbins & Han's (2006) 'decisional' account. Experiment 1 of our prior ERP study (Hayama et al., 2008; see Introduction) employed a procedure identical to that employed here, and demonstrated an analogous pattern of results. A robust right frontal ERP old/new effect, a putative neural correlate of post-retrieval monitoring, was elicited by correctly judged old items in both tasks, and was indistinguishable in respect of its magnitude and scalp distribution. It is important to note, however, that both these prior ERP findings and the findings from the present study are also compatible with the proposal that right DLPFC activity reflects the engagement of processes supporting post-retrieval monitoring (Henson et al., 2000; Rugg et al., 2003; Rugg, 2005), so long as this construct is extended to encompass the monitoring of information retrieved from episodic *and* semantic memory [and, arguably, lexical (Dobbins & Han, 2006) and perceptual (Fleck et al., 2006) information also].

A clear prediction of Dobbins & Han's (2006) decisional account is that neither the accuracy of an associated judgment nor the content of retrieved information should influence the engagement of right DLPFC. An obvious way to test this prediction is to contrast the effects elicited by items associated with correct vs. incorrect judgments. Unfortunately, the very small numbers of error trials in the present study preclude such an analysis. Thus the present data cannot be used to arbitrate between the foregoing 'decisional' and 'monitoring' accounts of right DLPFC engagement.

In addition to right DLPFC, old/new effects common to the two retrieval tasks were identified in left prefrontal regions that overlapped with regions demonstrating retrieval success effects in numerous prior event-related fMRI studies (for reviews see: Fletcher & Henson, 2001; Ranganath & Blumenfeld, 2008). These regions included left anterior prefrontal cortex, left ventral and dorsal aspects of the left inferior frontal gyrus (IFG), and a small region of left DLPFC. Old>new effects in left ventral IFG have previously been implicated in 'retrieval cue specification' (Dobbins et al., 2002) a process by which semantic relations between retrieval cues and potential sources are derived in order to facilitate retrieval (Fletcher & Henson, 2001). Since the source-specifying information retrieved in the source task was conceptual (pertaining to the semantic classification that was made at study), ventral IFG activity in association with old test items in that task is, arguably, to be expected. In addition, considerable evidence indicates that left ventrolateral PFC is involved more generally in the controlled retrieval of semantic information (see for review Badre & Wagner, 2007). Whereas the semantic test task may not have required the engagement of cue specification processes as defined above, it did of course require retrieval of the semantic features of old test items and it is this, presumably, that accounts for the ventral IFG old/new effects elicited in this task.

Activity in left lateral and anterior PFC has also been linked more generally to processes engaged by successful recognition memory, regardless of whether recognition was associated with retrieval of episodic details or was solely based on an acontextual sense of familiarity (Henson et al., 1999a; Ranganath, Johnson and D'Esposito, 2000; Konishi et al., 2000; Dobbins et al., 2002; Yonelinas et al., 2005). The functional significance of these left frontal old/new effects is unclear (see Herron et al., 2004 for evidence that the effects reverse when new items are made more salient than old items). It has been suggested, however, that old/new effects in left DLPFC reflect post-retrieval monitoring of conceptual information (Dobbins et al., 2002). To the extent this account of left DLPFC retrieval success effects is correct, the present findings imply that, as appears to be the case for right DLPFC, monitoring operations supported by left DLPFC are indifferent to whether information is derived from episodic or semantic memory.

In addition to the PFC, old/new effects common to the two tasks were also evident in superior parietal cortex in the vicinity of the intra-parietal sulcus. Old/new effects in this region are invariably reported in event-related fMRI studies of recognition memory and related tasks (for reviews see: Rugg and Henson, 2002; Vilberg & Rugg, 2008; Cabeza et al., 2008; Ciaramelli et al., 2008), and may reflect the greater 'target value' of old than new items (Vilberg and Rugg, 2008). Hence the finding that left superior parietal effects were evident in both cases is unsurprising. Old/new effects are also often identified in a more inferior lateral parietal region, in the vicinity of the angular gyrus (BA39). There is some agreement that these effects are associated specifically with retrieval of specific episodic details (recollection), although there is disagreement about their precise functional significance (cf. Cabeza et al., 2008; Vilberg and Rugg, 2008). In light of the necessity for successful recollection for accurate source judgments, left inferior parietal old/new effects should be especially prominent in the present source task. This was indeed the case; whereas inferior parietal old/new effects were not identified in the contrasts that focused on effects common to the two tasks, or in the task $\times$ old/new interaction contrast, they were evident in the old > new contrast for the source task alone (see figure 1B). The outcome of this contrast survived small volume correction using Gaussian random field theory for a 3 mm sphere centered on the center of mass of the recollection-related old > new effects reviewed in the meta-analysis of Vilberg and Rugg (2008).

New > Old Effects—In addition to the old > new effects discussed above, widespread new > old effects common to the two tasks were also evident. One especially prominent effect was identified in medial prefrontal cortex. This region has been implicated as belonging to the 'default mode' network (Raichle et al., 2001; Gusnard et al., 2001; Harrison et al., 2008), a network of regions that demonstrates 'task-related deactivations' (Buckner et al., 2008). Thus, given that responses were some 500ms faster to new than to old test items, the present medial frontal new > old effects are likely a consequence of the fact that subjects disengaged from the test trials, and hence 'restored' default activity, sooner for new than for old items.

Extensive new > old effects were also identified in bilateral MTL, centering on the hippocampus and extending anteriorly on the right into perirhinal cortex. Similar findings have been reported previously in studies of yes-no recognition memory (Rombouts et al., 2001), continuous recognition memory (Johnson, Muftuler, & Rugg, 2008; Yassa & Stark, 2008) and source memory (Rugg et al., 2003). New > old effects in perirhinal cortex have been interpreted as a familiarity signal (Henson et al., 2003; Aggleton & Brown, 2006), whereas new > old effects in hippocampus and parahippocampal cortex are held to reflect greater levels of encoding for new than for old items (Okado & Stark, 2003). The present findings are consistent with these accounts, although they offer no additional support in their favor. One reason why MTL new > old effects were so prominent in the present study (and that of Rugg et al., 2003) is suggested by the findings of Dudukovic and Wagner (2007). These authors reported that MTL activity was enhanced when item novelty was the task-relevant feature relative to a task where

novelty was irrelevant, suggesting that novelty-related MTL activity is modulated by goal-directed attention. The strategy of familiarity-gated recollection employed in the present task likely enhanced the utility of detecting novel test items, leading to a potentiation of novelty-related MTL activity analogous to that reported by Dudukovic and Wagner (2007).

Relationship between fMRI and ERP findings

The present study employed an experimental procedure virtually identical to Experiment 1 of our previous ERP study (Hayama et al., 2008). In that study, we reported that a putative ERP correlate of post-retrieval monitoring, the right frontal old/new ERP effect, was indistinguishable between the two tasks. This result fits well with the present finding of comparable right DLPFC old>new effects in the source and semantic tasks, and adds weight to prior suggestions that the ERP and fMRI effects reflect modulation of a common neural population (Rugg et al., 2002; Friedman et al., 2000). It should be noted, however, that as in numerous previous fMRI studies of recognition and source memory, extensive old>new effects were also evident in left PFC. As was discussed by Rugg et al., (1999) and Rugg et al., (2002), it is unclear why these left-lateralized fMRI effects have no obvious ERP parallel.

Concluding Comments

The current findings add to the evidence that retrieval-related activity in right DLPFC is not engaged selectively by the requirement to monitor the products of an episodic retrieval attempt. One possibility is that retrieval-related activity in this region is a function of the number of internal decisions that precede response selection (Dobbins & Han, 2006). Alternatively, the findings may point to a role for right DLPFC in 'post-retrieval' monitoring more generally. Indeed, it may be that once it has been retrieved, episodic information is processed in much the same way as information derived from a stimulus event in real time.

Acknowledgments

This research was supported by NIMH grant R01-MH072966. We thank the members of the UCI Research Imaging Center for their assistance with fMRI data acquisition.

References

- Aggleton JP, Brown MW. Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences* 2006;10(10):455–63. [PubMed: 16935547]doi:S1364–6613(06)00193-8
- Andrade A, Paradis AL, Rouquette S, Poline JB. Ambiguous results in functional neuroimaging data analysis due to covariate correlation. *NeuroImage* 1999;10(4):483–6. [PubMed: 10493904]doi: 10493904
- Badre D, Wagner AD. Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 2007;45(13):2883–901. [PubMed: 17675110]doi:S0028–3932(07)00221-7
- Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox. *NeuroImage* 2002;16:2.
- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* 2008;1124:1–38. [PubMed: 18400922]doi:1124/1/1
- Cabeza R, Ciaramelli E, Olson IR, Moscovitch M. The parietal cortex and episodic memory: an attentional account. *Nature Reviews Neuroscience* 2008;9(8):613–25.doi:nrn2459
- Ciaramelli E, Grady CL, Moscovitch M. Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia* 2008;46(7): 1828–51. [PubMed: 18471837]doi:S0028–3932(08)00110-3
- Cocosco C, Kollokian V, Kwan RS, Evans A. Brainweb: Online interface to a 3D MRI simulated brain database. *NeuroImage* 1997;5:S425.

- Dobbins IG, Foley H, Schacter DL, Wagner AD. Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron* 2002;35(5):989–96. [PubMed: 12372291]doi:12372291
- Dobbins IG, Han S. Isolating rule- versus evidence-based prefrontal activity during episodic and lexical discrimination: a functional magnetic resonance imaging investigation of detection theory distinctions. *Cerebral Cortex* 2006;16(11):1614–22. [PubMed: 16400153]doi:bhj098
- Dudukovic NM, Wagner AD. Goal-dependent modulation of declarative memory: neural correlates of temporal recency decisions and novelty detection. *Neuropsychologia* 2007;45(11):2608–20. [PubMed: 17499318]doi:S0028–3932(07)00085-1
- Fleck MS, Daselaar SM, Dobbins IG, Cabeza R. Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and nonmemory tasks. *Cerebral Cortex* 2006;16(11):1623–30. [PubMed: 16400154]doi:bhj097
- Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 2001;124(Pt 5):849–81. [PubMed: 11335690]doi:11335690
- Friedman D, Johnson R. Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. *Microscopy Research and Technique* 2000;51(1):6–28. [PubMed: 11002349]doi:11002349
- Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 1995;2:189–210.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. *NeuroImage* 1998;7(1):30–40. [PubMed: 9500830]doi:9500830
- Friston KJ, Glaser DE, Henson RNA, Kiebel S, Phillips C, Ashburner J. Classical and Bayesian inference in neuroimaging: applications. *NeuroImage* 2002;16(2):484–512. [PubMed: 12030833]doi:12030833
- Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98(7):4259–64. [PubMed: 11259662]doi:11259662
- Harrison BJ, Pujol J, López-Solà M, Hernández-Ribas R, Deus J, Ortiz H, et al. Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Sciences of the United States of America* 2008;105(28):9781–6. [PubMed: 18621692]doi:PMC2474491
- Hayama HR, Johnson JD, Rugg MD. The relationship between the right frontal old/new ERP effect and post-retrieval monitoring: specific or non-specific? *Neuropsychologia* 2008;46(5):1211–23. [PubMed: 18234241]doi:S0028–3932(07)00390-9
- Henson RN, Rugg MD, Shallice T, Dolan RJ. Confidence in recognition memory for words: dissociating right prefrontal roles in episodic retrieval. *Journal of Cognitive Neuroscience* 2000;12(6):913–23. [PubMed: 11177413]doi:11177413
- Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ. Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *The Journal of Neuroscience* 1999a;19(10):3962–72. [PubMed: 10234026]doi:10234026
- Henson RN, Shallice T, Dolan RJ. Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain* 1999b;122(Pt 7):1367–81. [PubMed: 10388802]doi:10388802
- Herron JE, Henson RNA, Rugg MD. Probability effects on the neural correlates of retrieval success: an fMRI study. *NeuroImage* 2004;21(1):302–10. [PubMed: 14741668]doi:14741668
- Johnson JD, Muftuler LT, Rugg MD. Multiple repetitions reveal functionally and anatomically distinct patterns of hippocampal activity during continuous recognition memory. *Hippocampus* 2008;18(10):975–80.10.1002/hipo.20456 [PubMed: 18548578]
- Kahn I, Davachi L, Wagner AD. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *The Journal of Neuroscience* 2004;24(17):4172–80. [PubMed: 15115812]doi:15115812
- Konishi S, Wheeler ME, Donaldson DI, Buckner RL. Neural correlates of episodic retrieval success. *NeuroImage* 2000;12(3):276–86. [PubMed: 10944410]doi:10944410

- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98(2):676–82. [PubMed: 11209064]doi:PMC14647
- Ranganath C, Johnson MK, D'Esposito M. Left anterior prefrontal activation increases with demands to recall specific perceptual information. *The Journal of Neuroscience* 2000;20(22):RC108. [PubMed: 11069977]doi:11069977
- Ranganath, C.; Blumenfeld, RS. Prefrontal Cortex and Memory. In: Eichenbaum, H.; Byrne, JH., editors. *Learning and Memory: A Comprehensive Reference*. London: Academic; 2008. p. 261-279. Chapter 3.14
- Rombouts SA, Barkhof F, Witter MP, Machielsen WC, Scheltens P. Anterior medial temporal lobe activation during attempted retrieval of encoded visuospatial scenes: an event-related fMRI study. *NeuroImage* 2001;14(1 Pt 1):67–76. [PubMed: 11525338]doi:11525338
- Rugg MD, Allan K, Birch CS. Electrophysiological evidence for the modulation of retrieval orientation by depth of study processing. *Journal of Cognitive Neuroscience* 2000;12(4):664–78. [PubMed: 10936918]doi:10936918
- Rugg MD, Fletcher PC, Chua PM, Dolan RJ. The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. *NeuroImage* 1999;10(5):520–9. [PubMed: 10547329]doi:10547329
- Rugg MD, Henson RNA, Robb WGK. Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. *Neuropsychologia* 2003;41(1):40–52. [PubMed: 12427564]doi:12427564
- Rugg MD, Otten LJ, Henson RNA. The neural basis of episodic memory: evidence from functional neuroimaging. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences* 2002;357(1424):1097–110. doi:12217177
- Rugg MD, Wilding EL. Retrieval processing and episodic memory. *Trends in Cognitive Science* 2000;4(3):108–115.
- Rugg, MD. Retrieval processing in human memory: Electrophysiological and fMRI evidence. In: Gazzaniga, MS., editor. *The Cognitive Neurosciences III*. Cambridge, MA: MIT Press; 2005. p. 727-737.
- Senkfor AJ, Van Petten C. Who said what? An event-related potential investigation of source and item memory. *Journal of Experimental Psychology Learning, Memory, and Cognition* 1998;24(4):1005–25. doi:9699305
- Stark CEL, Okado Y. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *The Journal of Neuroscience* 2003;23(17):6748–53. [PubMed: 12890767]doi:12890767
- Ullsperger M, Mecklinger A, Müller U. An electrophysiological test of directed forgetting: the role of retrieval inhibition. *Journal of Cognitive Neuroscience* 2000;12(6):924–40. [PubMed: 11177414]doi:11177414
- Van Petten C, Senkfor AJ, Newberg WM. Memory for drawings in locations: spatial source memory and event-related potentials. *Psychophysiology* 2000;37(4):551–64. [PubMed: 10934914]doi:10934914
- Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. *Neuropsychologia* 2008;46(7):1787–99. [PubMed: 18343462]doi:S0028–3932(08)00015-8
- Wilding EL, Rugg MD. An event-related potential study of recognition memory with and without retrieval of source. *Brain* 1996;119(Pt 3):889–905. [PubMed: 8673500]doi:8673500
- Yassa MA, Stark CEL. Multiple signals of recognition memory in the medial temporal lobe. *Hippocampus* 2008;18(9):945–54. 10.1002/hipo.20452 [PubMed: 18493928]
- Rugg, MD.; Henson, RNA. Episodic memory retrieval: an (event-related) functional neuroimaging perspective. In: Parker, AE.; Wilding, EL.; Bussey, T., editors. *The cognitive neuroscience of memory encoding and retrieval*. Psychology Press; 2002.
- Yonelinas AP, Otten LJ, Shaw KN, Rugg MD. Separating the brain regions involved in recollection and familiarity in recognition memory. *The Journal of Neuroscience* 2005;25(11):3002–3008. [PubMed: 15772360]

Figure 1.

A: Regions identified with the early HRF where retrieval success (old>new) effects ($p < .001$) were common to the two tasks, overlaid on a rendered canonical brain. These regions included (i) Left anterior prefrontal cortex, (ii) Left inferior/middle frontal gyrus, and (iii) left superior parietal cortex. Graphs depict mean parameter estimates (arbitrary units) and standard errors of activity in the peak voxels (MNI coordinates) for each cluster. ** $p < 0.005$; *** $p < 0.001$

B: Retrieval success effects common to the two task (Green), displayed with success effects from the source task alone (Red). Overlapping regions are shown in yellow. Data are displayed on a sagittal section a ($x = -46$) of a canonical MNI template brain (all effects thresholded at $p < .001$).

Figure 2.

Regions identified with the late HRF where retrieval success effects were common to the two tasks, overlaid on a rendered canonical brain. Bar graph shows the peak parameter estimates (arbitrary units) and standard errors for the peak voxel of the right DLPFC cluster; ** $p < 0.005$; *** $p < 0.001$. Also illustrated are the time courses of the BOLD responses averaged within a 5mm radius sphere centered on the peak voxel of the right DLPFC cluster for each class of test items. The x- and y- axis units are in seconds and percent signal change, respectively.

Figure 3.

Regions identified with the early HRF where activity was greater for correct rejections than for hits (new>old effects) regardless of task. Effects are displayed on coronal and sagittal sections of the across-subject mean of the normalized T₁-weighted images. Graphs depict mean parameter estimates (arbitrary units) and standard errors of activity in the indicated peak voxels (MNI coordinates). * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$.

Table 1

Mean (SD) proportions and RTs (in ms) for each response type in the two test tasks

Proportions (S.D)		RT (S.D.)
Semantic	Correct	0.81 (0.16)
	Incorrect	0.11 (0.11)
	New	0.96 (0.03)
Source	Correct	0.71 (0.13)
	Incorrect	0.17 (0.10)
	New	0.97 (0.04)

Superscript letter 'a' denotes that RT data are based on 13 subjects. The excluded subjects made no incorrect responses

Table 2
Cortical regions demonstrating Old > New effects common to both tasks

Region	BA	Coordinates			Z-values # of voxels		
		x	y	z			
Early							
L Inferior Frontal Gyrus	9	-57	12	33	5.51	154	
L Anterior prefrontal	10	-24	54	-3	4.03	18	
L Medial Frontal Gyrus	6	-9	15	51	4.65	47	
L Medial Frontal Gyrus	6	-3	33	39	3.94	32	
L Thalamus		-9	-18	6	4.77	24	
L Inferior Parietal Lobe	7/40	-45	-60	54	3.99	13	
L Inferior Parietal Lobe	7/40	-48	-48	57	4.81	150	
L Inferior Temporal Gyrus	20	-63	-51	-18	3.66	11	
R Middle Frontal Gyrus	6	36	9	60	3.66	12	
R Inferior Parietal Lobe	7/40	42	-57	42	3.62	55	
Late							
L Inferior Temporal Gyrus	20	-63	-51	-18	4.27	19	
L Anterior Prefrontal	10	-33	60	-6	4.10	48	
L Ventrolateral Prefrontal	47	-39	45	-18	3.62	9	
R Anterior Prefrontal	10	27	57	-9	3.70	10	
R Dorsolateral Prefrontal	9/46	57	24	27	3.46	15	
R Cuneus	17/18	12	-78	6	3.40	15	

Data are shown separately for early and late HRFs

Table 3
Cortical regions demonstrating New > Old effects common to both tasks

Region	BA	Coordinates			Z-values # of voxels
		x	y	z	
Early					
L Middle Occipital Gyrus	19	-36	-96	9	4.26 388
L Hippocampus		-21	-12	-18	4.22 243
L Cingulate Gyrus	24/31	-3	-9	42	4.37 155
L Cingulate Gyrus	31	-15	-33	39	4.00 59
L Precentral Gyrus	3/4	-15	-33	75	3.97 54
L Superior Temporal Gyrus	41/42	-51	-33	9	3.70 21
L Superior Temporal Gyrus	21/22	-57	-3	6	3.57 34
L Insula	13/22	-39	-27	-9	3.53 18
Medial Frontal Gyrus	10/32	-9	39	-3	5.54 1555
Medial Frontal Gyrus	6	0	-24	60	3.38 22
R Insula	13	33	0	18	3.78 42
R Inferior Frontal Gyrus	47	27	24	-24	3.72 31
R Middle Temporal Gyrus	20/21	48	-3	-36	4.86 213
R Inferior Frontal Gyrus	45/47	51	36	-3	4.22 39
R Hippocampus		27	-9	-21	4.76 105
R Middle Occipital Gyrus	19	36	-90	21	5.08 1174
Late					
L Superior Frontal Gyrus	6	-21	0	54	3.86 18
L Inferior Temporal Gyrus	20/21	-54	-3	-30	3.41 11
L Medial Frontal Gyrus	10/11	-9	39	-9	4.34 214
L Subcallosal Gyrus	25	-3	15	-9	4.16 87
L Posterior Cingulate	23/31	-6	-57	18	3.89 70
L Parahippocampal Gyrus	28/35	24	-21	-21	3.57 14

Data are shown separately for early and late HRFs

Table 4
Cortical regions demonstrating Old/New effects greater in the source than semantic task

Region	BA	Coordinates			Z-values # of voxels	
		x	y	z		
L Inferior Frontal Gyrus	45/46	-48	33	3	3.68	13
L Precuneus	7	-9	-75	45	3.66	29
L Inferior Parietal Lobe	7	-33	-69	48	3.42	11
R Superior Frontal Gyrus	6/8	6	21	60	3.45	11