Going Their Separate Ways: Dissociation of Hippocampal and Dorsolateral Prefrontal Activation during Episodic Retrieval and Post-retrieval Processing

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Abstract

■ Hippocampal activity is modulated during episodic memory retrieval. Most consistently, a relative increase in activity during confident retrieval is observed. Dorsolateral prefrontal cortex (DLPFC) is also activated during retrieval, but may be more generally activated during cognitive-control processes. The "default network," regions activated during rest or internally focused tasks, includes the hippocampus, but not DLPFC. Therefore, DLPFC and the hippocampus should diverge during difficult tasks suppressing the default network. It is unclear, however, whether a difficult episodic memory retrieval task would suppress the default network due to difficulty or activate it due to internally directed attention. We hypothesized that a task requiring episodic retrieval followed by rumination on the retrieved item would increase DLPFC activity, but paradoxically reduce hippocampal activity due to concomitant suppression of the default network. In the present study, blocked and event-related fMRI were used to examine hippocampal activity during episodic memory recollection and postretrieval processing of paired associates. Subjects were asked to make living/nonliving judgments about items visually presented (classify) or items retrieved from memory (recall–classify). Active and passive baselines were used to differentiate task-related activity from default-network activity. During the "recall–classify" task, anterior hippocampal activity was selectively reduced relative to "classify" and baseline tasks, and this activity was inversely correlated with DLPFC. Reaction time was positively correlated with DLPFC activation and default-network/hippocampal suppression. The findings demonstrate that frontal and hippocampal activity are dissociated during difficult episodic retrieval tasks and reveal important considerations for interpreting hippocampal activity associated with successful episodic retrieval. ■

INTRODUCTION

Memory recollection is seldom independent of other cognitive processes that are called upon to perform routine activities. Rather, memory retrieval is recruited alongside several processes working in concert to perform everyday tasks. Often, the products of recollection are held in mind for some time while further cognitive processing occurs (Daselaar et al., 2008; Buckner, 2003; Wagner, Maril, Bjork, & Schacter, 2001; Moscovitch, 1992). When an item is retrieved from memory, working memory (WM) processes may be called upon to both monitor the validity of the memory retrieved (postretrieval monitoring; Rugg & Wilding, 2000) and perform processes necessary in pursuit of a cognitive task. Thus, interplay between long-term memory (LTM) and WM may be required to perform many real-world tasks that involve postretrieval processing.

Similarly, tasks designed to gauge memory strength involve postretrieval processing as subjects ruminate on the products of retrieval to determine whether the item was strongly or weakly recognized. Prior imaging studies have shown increases in hippocampal activity during successful LTM retrieval. Retrieval of information from LTM activates the hippocampus particularly when items have been deeply encoded (Weis et al., 2004; Dobbins, Rice, Wagner, & Schacter, 2003; Greicius et al., 2003; Ranganath & Rainer, 2003; Zeineh, Engel, Thompson, & Bookheimer, 2003; Dolan & Fletcher, 1997; Gabrieli, Brewer, Desmond, & Glover, 1997; Schacter et al., 1995) and recollection is made with high confidence or is associated with retrieval of additional details of the encoding event (Davachi, Mitchell, & Wagner, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000).

It is unclear how brain imaging results are influenced by the additional component of postretrieval processing included in studies where subjects make confidence judgments. Interpretation of hippocampal activity during these tasks is further complicated by the fact that the hippocampus is part of the default network, an interconnected set of brain regions that are active during mind wandering (Mason et al., 2007) or during internally directed thought (Esposito et al., 2006; Fransson, 2006; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001).

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Thus, these regions are often maximally deactivated during more difficult tasks requiring an external focus of attention. Indeed, activity in medial temporal lobe (MTL) regions, specifically the posterior parahippocampus, has been shown to be reduced by active versus passive nonmnemonic tasks (Stark & Squire, 2001). On the other hand, recognition tasks activate a set of "retrieval network" brain regions that overlap with the default network, including the precuneus, posterior cingulate, retrosplenial cortex, and lateral parietal cortex (Buckner & Vincent, 2007; Vincent et al., 2006). It is plausible that making and judging a confident recognition of an item may be quicker and easier than making and judging a less confident recognition of an item. Thus, there is an alternative interpretation of increased retrieval network and hippocampal activity during confident recollection; confident recollection judgments lead to less suppression of the default network than do judgments of familiarity.

Activity in dorsolateral prefrontal cortex (DLPFC) may be related less to retrieval itself than to cognitive control or postretrieval monitoring. Prior studies have found that activity in DLPFC is not directly tied to retrieval mode (Kapur et al., 1995) or to retrieval success (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996). Henson, Rugg, Shalice, and Dolan (2000) found increased activity in right DLPFC for low-confidence judgments, which require more monitoring before a decision is made. In a nonmnemonic task, Fleck, Daselaar, Dobbins, and Cabeza (2006) found that DLPFC activity is not based on continuous monitoring, but rather is dependent on discontinuous evaluation of ongoing events.

No prior imaging studies have directly addressed frontal and hippocampal activity dissociations during episodic memory retrieval and postretrieval processing. However, studies of active memory suppression have shown inversely correlated activity in these two regions, suggesting a dynamic interplay between frontal and hippocampal regions at retrieval (Depue, Curran, & Banich, 2007; Anderson et al., 2004). An episodic retrieval task that requires subjects to make a judgment on the products of retrieval might be expected to similarly activate DLPFC and suppress hippocampal regions if the default network is driven more generally by task difficulty. The opposite result would be expected if the default network is active during internally directed thought, including memory retrieval processes and postretrieval rumination. To test these competing hypotheses, we included active and passive baselines in our studies of memory recall to identify classic default network suppression and compare it to suppression associated with the memory task.

To directly investigate frontal and hippocampal memory dissociations during episodic memory retrieval and postretrieval processing, the present study examined frontal and hippocampal interaction during retrieval of information from LTM and further classification of that information. This task was contrasted with a task in which subjects classified items that were visually presented. Subjects were asked to make living/nonliving judgments about items retrieved from memory (recall–classify), and in a control task, subjects made living/nonliving judgments on visually presented items (classify). In addition, active (odd/even digit classification) and passive (fixation) baselines were used, allowing comparison of the task to different baselines that have been shown to influence MTL activity. Based on studies that suggest recruitment of frontal lobe circuitry in postretrieval processing (Moscovitch, 1992), we expected to see greater recruitment of DLPFC during a task that required postretrieval classification than during simple classification of items visually presented. We predicted that this activity would be correlated with trial-by-trial reaction time (RT) and expected default-network regions/hippocampus to show the inverse pattern of activity.

A block-design experiment revealed increased DLPFC activity and suppressed hippocampal activity during the recall–classify task. This hippocampal region showed no difference in activity during even/odd discrimination, fixation, and classify tasks. To further examine the temporal basis of the observed hippocampal suppression, a rapid event-related design was used to replicate the findings and explore the time course of the activity. The time course was then separated based on RT within each task type, showing that DLPFC is more active and the hippocampus is more suppressed during memory recall trials with longer RTs.

METHODS

Subjects

Twenty-two healthy right-handed subjects were recruited from the University of California, San Diego, community and the surrounding area. Twelve subjects (mean age = 23.83 ± 3.01 years, 5 men) participated in Experiment 1 and 10 subjects (mean age = 22.75 ± 3.37 years, 5 men) participated in Experiment 2. Two subjects (male) were excluded from Experiment 2 due to scanner and response-recording device technical issues. Subjects were paid $40 for their participation and gave informed consent approved by the Institutional Review Board of the University of California, San Diego.

Stimuli

Stimuli were 256 color drawings of common objects selected from Rossion and Pourtois (2004) color Snodgrass images. Drawings were paired randomly into 128 pairs. Pairs were screened to remove those with obvious visual or semantic relationships.

Experiment 1: Block Design

Experiment 1 examined magnetic resonance BOLD response during classification judgments made on items

retrieved from LTM (recall–classify) or items visually presented (classify). In addition, active (even/odd discrimination) and passive (fixation) baselines were assessed. Prior to the scan, subjects learned pairs of images using a study task that provided a high degree of retrieval accuracy in a behavioral pilot (range: 70–93% correct). During this study phase of the experiment, which took place approximately 30 min before scanning, subjects saw 128 pairs of items and were instructed to remember which items were paired together. Two images were presented side-by-side for 3 sec, and each pair of items was presented three times during the course of the study session.

During scanning, subjects were presented with two adjacent noise-mask-filled boxes on the viewing screen, one outlined in black and one outlined in either red or green (Figure 1). After 1 sec, a single image from the study set appeared in either the black or the green box for 0.5 sec. The green box indicated that the subject should classify the presented item as "living" or "nonliving." The red box indicated that the subject should recall and classify the pair of the presented item. Subjects were given 1.5 sec to make a judgment of "living" or "nonliving" for each image seen (green trial) or recalled (red trial) and were instructed not to respond if unable to recall the item. "Recall–classify" and "classify" blocks each included eight trials of one condition, and these were interspersed with blocks of 16 odd/even judgments (1.5 sec each) or 24 sec of fixation cross. There were four blocks of each condition in each of 4 runs. Runs lasted 395 sec, and were separated by 2- to 3-min breaks.
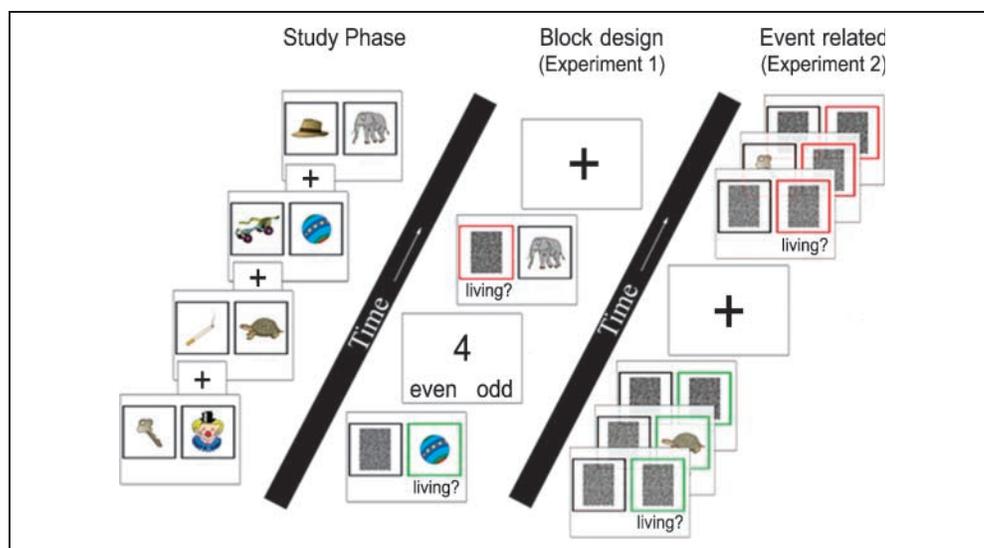
Block-design fMRI Data Analysis

Using the AFNI (Cox, 1996) suite of programs, data from each run were reconstructed. Slices were temporally aligned and coregistered with a 3-D registration algorithm. Voxels outside the brain were removed using a threshold mask of the functional data. Functional runs were corrected for

motion and concatenated. For each of the four conditions, the raw signal was averaged from 9 to 24 sec of each 24-sec block for all 12 subjects. The initial 9 sec were excluded to avoid confounds from the previous block. The 16 blocks of each condition were then averaged together to get one average activation trace at each voxel for each of the four conditions. Standard landmarks were defined manually on the anatomical scans, and then the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998) using AFNI nearest neighbor interpolation (Cox, 1996). Voxelwise t tests (two-tailed) were performed to compare average BOLD signal across conditions. Because of the small volume of our area of interest (hippocampus), clusters were defined with a connectivity of 4 mm between voxel centers and including at least 5 voxels (for a whole-brain corrected p value of .05). AlphaSim was used to correct for multiple comparisons inside the brain and to obtain cluster significance. Clusters consisting of voxels significant at $p < .001$ (corrected for multiple comparisons) were displayed on a statistical map overlaid onto an average structural image and were used to extract average activity in each region.

Experiment 2: Event-related

To replicate and further explore the time course of task-related activity elicited by the block-design study, an event-related design was used to examine frontal and hippocampal activity during the recall–classify and classify conditions contrasted with a fixation baseline. In this study, subjects had a study session identical to the block-design study and were asked to perform the recall–classify, classify, and fixation tasks in the scanner. During scanning, subjects were presented with two adjacent noise-mask-filled boxes on the viewing screen, one outlined in black and one outlined in either red or green (Figure 1). After 0.5 sec, an image appeared in either the

Figure 1. Study design. Each subject viewed the study phase outside of the scanner. Subjects were asked to memorize 128 pairs of images that were shown three times each. During scanning, subjects performed the block task in which recall–classify, classify, even/odd, and fixation cross trials were presented in blocks lasting 24 sec each. In Experiment 2, subjects performed the event-related task in which recall–classify, classify, and fixation trials were interleaved. Red box = recall–classify; Green box = classify.

black or the green box for 0.5 sec. Instructions were identical to those of the block experiment. Subjects were asked to make a judgment of "living" or "nonliving" for each image seen or recalled (2 sec), and to respond with "unsure" if they could not recall the pair. Error trials (unsure, incorrect, and no response) were excluded from the analysis. Trials were jittered with 0, 1.5, 3, or 4.5 sec of fixation baseline. Each subject underwent a single session of four scans lasting 362 sec each.

Event-related fMRI Data Analysis

Data from each run were reconstructed. Slices were temporally aligned and coregistered with a 3-D registration algorithm. Voxels outside the brain were removed using a threshold mask of the functional data. Functional runs were corrected for motion. A general linear model was constructed using multiple regression analysis, and included six motion regressors from the registration process and regressors for recall–classify and classify condition correct and incorrect responses. Standard landmarks were defined manually on the anatomical scans, and then the anatomical and functional scans were transformed into Talairach space (Talairach & Tournoux, 1998) using AFNI nearest neighbor interpolation (Cox, 1996). For the recall–classify and classify conditions, a hemodynamic response was estimated for the 15 sec following the onset of the stimulus using signal deconvolution. Voxelwise t tests (two-tailed) were performed to compare average BOLD signal between conditions. Because of the small volume of our area of interest (hippocampus), clusters were defined with a connectivity of 4 mm between voxel centers and including at least 5 voxels. These clusters, significant at $p < .05$ (two-tailed and corrected for multiple comparisons) were displayed on a statistical map overlaid onto an average structural image, and the average hemodynamic response function was then extracted for each cluster of interest.

Correlation Analysis

The time course of the seed region of interest was extracted and a contrast regressor for recall–classify and classify conditions was obtained to construct the interaction regressor (Heekeren, Marrett, Bandettini, & Ungerleider, 2004). The first-order regressor of the hemodynamic response function for each task and the second-order regressor of the interaction are both necessary for a context-dependent correlation analysis. These regressors were obtained by using the design matrix to isolate activity related to recall–classify and classify trials for each subject. The resulting time courses for voxels within the seed region were averaged, and the product of this time course and the contrast regressor was used as the interaction regressor for the final step of the correlation analysis. These regressors were used to obtain a map of regions correlated with the seed region for each subject. Correlation coefficients showed areas in the brain that were more correlated in the recall–classify task than in the classify task. Correlation coefficients were converted to Z-scores, analyzed with a t test, and clustered at a threshold of $p < .05$ (corrected for multiple comparisons).

Response Time Analysis

To further explore the event-related data, correct trials in the recall–classify and classify conditions were separated into two groups within each condition: 1) trials where the RT was $>+1$ standard deviation from the mean and 2) trials where the RT was <-1 standard deviation from the mean for each subject (see Table 1 for individual RT means and average SDs). For the recall–classify and classify conditions, a hemodynamic response was estimated for the 15 sec following the onset of the stimulus using signal deconvolution. Voxelwise t tests (two-tailed) were performed to compare average BOLD signal between long and short RT trials, separately analyzed in the recall–classify and classify conditions. The average hemodynamic response function was then extracted for the DLPFC and hippocampal clusters identified in the initial recall–classify minus classify contrast.

fMRI Parameters

Imaging was done in a 3-T GE scanner at the Keck Center for Functional MRI at the University of California, San Diego. Functional images were acquired using a gradient-echo, echo-planar, T2*-weighted pulse sequence (repetition time = 1.5 sec, one shot per repetition, echo time = 30, flip angle = 90°, bandwidth = 31.25 MHz). Twenty-two slices covering the entire brain were acquired perpendicular to the long axis of the hippocampus with 4 × 4 × 7 mm voxels, allowing greater summation of activity

Table 1. Mean Reaction Time (RT), Average of RT Standard Deviations (*SD*), Min RT, and Max RT for Recollect–Classify (RC) and Classify (C) Conditions for Each Subject

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
RC Mean RT	1475	1311	1679	1881	1327	1466	1669	1839
RC Average *SD*	267	297	410	355	296	384	447	430
RC Min	1006	934	1015	1205	773	934	884	787
RC Max	2147	2070	2416	2463	2063	2293	2423	2449
C Mean RT	937	964	986	1378	922	1107	950	1278
C Average *SD*	157	245	233	413	334	391	348	436
C Min	743	660	689	604	497	553	466	472
C Max	1442	1908	1769	2291	1880	2087	1899	2219

These average RT *SD*s were used to classify each trial as −3, −2, −1, 0, 1, 2, or 3 *SD*s from the mean RT for each subject individually.

along the hippocampal axial plane (Brewer & Moghekar, 2002). A T1-weighted high-resolution (1 × 1 × 1 mm), three-dimensional magnetization-prepared rapid gradient echo or fast spoiled gradient recalled anatomical dataset was collected. A structural scan was acquired in the same slice locations as the functional images for use in confirming alignment of functional data to the high-resolution anatomical scan.

RESULTS

Experiment 1: fMRI Results—Block

Behavioral Results

The mean RTs after the onset of the stimulus differed $[F(2, 33) = 22.41, p < .001]$ for the recall–classify condition (937 ± 57 msec), classify condition (484 ± 57 msec), and even/odd discrimination (677 ± 18 msec). Post hoc Bonferroni tests indicated that RT for the recall–classify task was significantly longer than for the classify task ($p < .01$) and even/odd discrimination ($p < .05$). RT for the classify task was significantly shorter than for even/odd ($p < .001$). Subjects responded in 73 ± 4% of trials for the recall–classify task and made correct judgments in 86 ± 2% of those trials. Subjects responded in 97 ± 1% of classify trials and made correct judgments in 98 ± 1% of those trials.

fMRI Results: Recall–Classify vs. Classify

As depicted in Figure 2, the bilateral anterior hippocampus showed BOLD responses that were significantly lower for recall–classify than for classify, even/odd, or fixation (each $p < .001$, corrected). In bilateral DLPFC (Brodmann's area 9), BOLD response was significantly higher for recall–classify than for classify, even/odd, and fixation ($p < .01$, corrected) and was higher for classify than for even/odd and fixation ($p < .05$, corrected). A list of clusters significantly different in the recall–classify and classify conditions at $p < .001$, corrected, can be found in Table 2.

fMRI Results: Correlation Analysis

Using the left hippocampus as a seed region, a correlation analysis was performed using recall–classify and classify tasks as regressors to determine areas of activity more correlated with the observed decrease in hippocampal activity during the recall–classify condition. The left and right hippocampus were positively correlated with each other and inversely correlated with bilateral DLPFC (Figure 3; $p < .05$, corrected). The hippocampus was positively correlated with the bilateral middle frontal gyrus as well as bilateral precentral and superior temporal gyri and was inversely correlated with bilateral fusiform, parahippocampal, anterior cingulate, and occipital gyri.

fMRI Results: Default Network

The even/odd minus fixation (EO–FIX) activation map of the present study shows activity decreases in the precuneus, posterior cingulate, and other midline structures, similar to prior published results describing "default-network" activity (i.e., areas that are more active for easier tasks) (for a list of significant clusters, see Table 3). Stark and Squire (2001) used an EO–FIX contrast to show that MTL regions may be part of the default network. A comparison between the present EO–FIX contrast and the Stark and Squire EO–FIX contrast reveals similar activity maps (Figure 4). Both studies show activation in the posterior parahippocampal regions in addition to posterior cingulate and other midline structures. Activation maps from

Figure 2. Experiment 1 BOLD activation. Difference in BOLD activation for significant clusters in the recall–classify versus classify condition ($p < .001$). (A) Activation in right DLPFC (37.4, 26.1, 30.3) for each condition. (B) Activation in the right anterior hippocampus (20.3, −9, −10.9) and (C) left anterior hippocampus (−25.4, −6.6, −12.3) for each condition. RC = recall–classify; C = classify; EO = even/odd discrimination; FIX = fixation. Error bars represent *SEM*. Interior clusters up to 29 mm deep are projected onto the surface and the color scale bar represents percent signal change. *$p < .05$, **$p < .01$, ***$p < .001$.
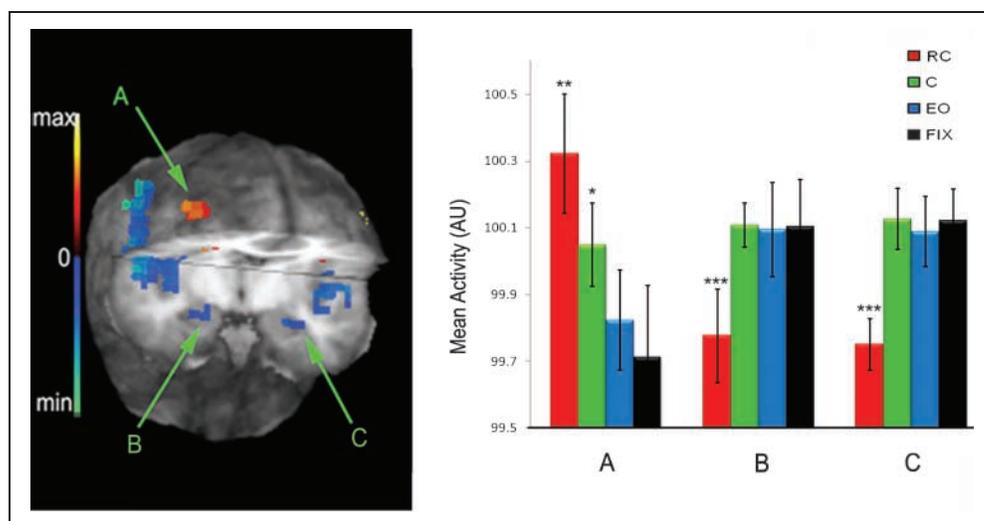
Table 2. Clusters Significant ($p < .001$) for Recall–Classify versus Classify Conditions

| | Talairach | | | | |
	x	y	z	Volume	t
(A) RC > C					
R. Cingulate gyrus (BA 32)	0.7	20.6	39.8	2624	7.20
L. DLPFC (middle frontal gyrus, BA 9)	−43.9	13.4	32.1	1728	7.57
L. Inferior parietal lobule (BA 39)	−33.1	−59.6	38.9	1664	7.35
R. Anterior insula (BA 13)	27.7	19.5	5.4	960	7.49
R. DLPFC (middle frontal gyrus, BA 9)	37.4	26.1	30.3	768	6.31
L. Anterior insula (BA 13)	−29.4	20.8	3.7	640	7.74
R. Precuneus (BA 7)	7.8	−67.5	40.5	512	5.01
R. Precuneus (BA 7)	24.7	−61.7	33.9	320	5.11
L. Cingulate gyrus (BA 32)	−10	24.9	30	256	4.86
L. Precuneus (BA 7)	−14.6	−66.8	30.8	256	5.71
(B) C > RC					
R. Insula (BA 13)	45.7	−14	16.7	9728	−8.74
L. Insula (BA 13)	−43.4	−11.1	4.9	5568	−8.88
R. Precentral gyrus (BA 4)	32.7	−27.9	50.4	2112	−10.06
L. Postcentral gyrus (BA 5)	−27.2	−39.7	61.2	1472	−8.28
L. Paracentral lobule (BA 6)	−2.2	−25.6	50.8	1280	−6.98
R. Superior parietal lobule (BA 5)	19.7	−39.6	58.6	832	−5.67
L. Postcentral gyrus (BA 40)	−50.2	−25	13.7	768	−7.91
R/L. Paracentral lobule (BA 31)	−2.7	−16.7	43	640	−7.60
L. Hippocampus (BA 34)	−25.4	−6.6	−12.3	576	−9.91
R. Postcentral gyrus (BA 2)	25.3	−36	66.9	512	−6.18
L. Precentral gyrus (BA 4)	−55.7	−12.8	33.1	448	−6.27
R. Hippocampus (BA 34)	20.3	−9	−10.9	256	−5.55

BA = Brodmann's area.

the EO–FIX contrast from the current experiment were compared to activation maps from the recall–classify versus classify contrast to determine regions of overlap between the default network and activation due to the experimental condition. To show that the current recall–classify versus classify contrast results in MTL activation distinct from the default network defined by EO–FIX, an overlap analysis was done comparing activations from the EO–FIX and recall–classify versus classify contrasts.

Comparison of the activation maps of recall–classify versus classify and EO–FIX revealed MTL regional suppression for the experimental conditions that was spatially distinct from that attributable to the default network defined by the contrast of EO–FIX (Figure 5). Whereas the recall–classify versus classify contrast revealed significant clusters in the bilateral anterior hippocampus, insular cortex, and DLPFC, the EO–FIX contrast revealed significant clusters in the posterior cingulate, insular cortex, and bilateral posterior parahippocampus. Although many of the regions commonly defined as part of the default network showed less activity in both of these contrasts, EO–FIX showed decreased activity in the posterior parahippocampus while a suppression of the anterior hippocampus was only observed in the task requiring memory retrieval. The overlap analysis showed no overlapping voxels in the MTL. This comparison reveals that the default-network-related modulation of MTL activity, which replicated the Stark and Squire (2001) findings, is different than the hippocampal suppression revealed by the recall–classify versus classify contrast.

Figure 3. Experiment 1: Hippocampal suppression and DLPFC activation are correlated during the recall–classify task. The left hippocampus (HC) was used as the seed region. The right hippocampus was correlated and bilateral DLPFC (BA 9) regions were anticorrelated with this seed region during the recall–classify task. Only HC and DLPFC clusters are shown.
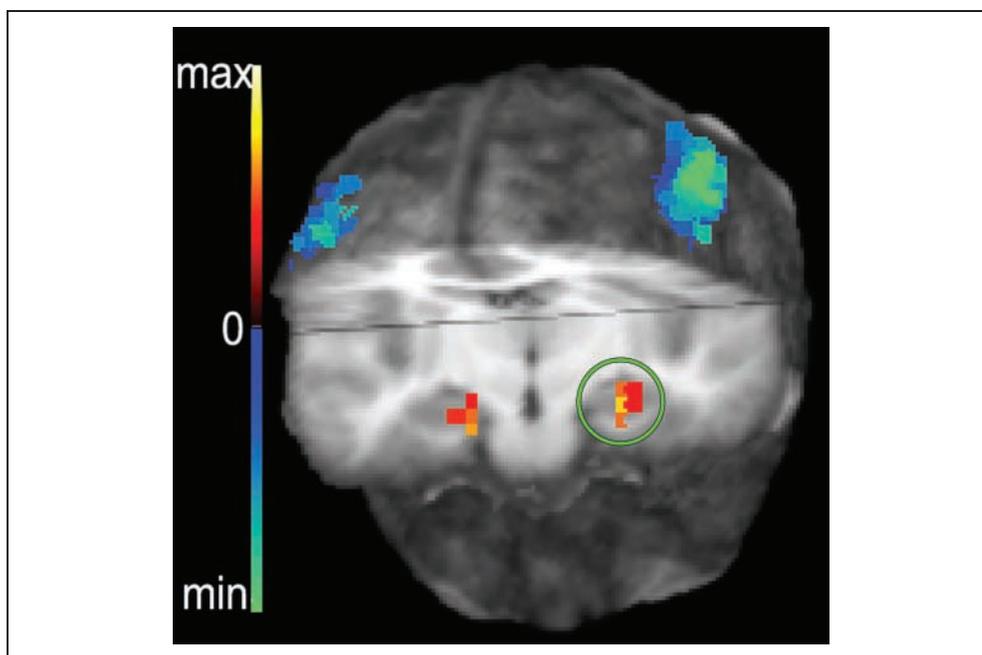
Experiment 2: fMRI Results—Event-related with Fixation Baseline

Behavioral Results

The mean RTs differed for recall–classify (1552 ± 69 msec) and classify (1060 ± 63 msec) conditions. RT for recall–classify was significantly longer than for classify [$t(7)$ = 8.54, $p < .001$]. Subjects responded in 80 ± 5% of trials for the recall–classify task and made correct judgments in 90 ± 1% of those trials. Subjects responded in 96 ± 1% of classify trials and made correct judgments in 97 ± 1% of those trials. Only these correct judgments were used in further analysis.

fMRI Results

Cluster maps of the difference in activation in the recall–classify and classify conditions showed significant differences ($p < .05$, corrected) in the right hippocampus and left DLPFC. The hippocampus showed less activation in the recall–classify condition, whereas DLPFC showed more activity during this task (Figure 6). These clusters were used as a mask to extract average impulse response curves for each subject, which revealed increases in DLPFC activity (Figure 6A, left) that corresponded to decreases in hippocampal activity (Figure 6B, left). As in Experiment 1, in a correlation analysis, activity in the right hippocampus was more anticorrelated with activity in DLPFC for the recall–classify condition than for the classify condition [$t(7)$ = 3.106, $p < .01$].

Clusters defined in the original contrast were used for further analysis within each trial type, and differences in the right hippocampus and left DLPFC for recall–classify and classify trials with longer and shorter RTs were examined. Left DLPFC (Figure 6A, right) showed greatest amounts of activation for the recall–classify trials with longer RTs, and intermediate activation for the recall–classify trials with shorter RTs. Activation in the classify trials with the longer RTs overlapped with activation for recall–classify trials with shorter RTs. DLPFC activation for the classify trials with the shorter RTs was lowest. The right hippocampus (Figure 6B, right) showed a decrease in activity for the long RT recall–classify trials versus short RT recall–classify trials. No such relationship between RT and hippocampal deactivation was noted for classify trials.

DISCUSSION

These experiments examined brain activity associated with memory retrieval followed by working with the information retrieved. During Experiment 1, BOLD activation in the anterior hippocampus was significantly reduced for recall–classify compared with classify, even/odd discrimination, and fixation. Hippocampal suppression was correlated with an increase in activity in DLPFC. In Experiment 2, the findings were replicated and extended to show the time course of hippocampal activity with a reduction of BOLD signal in the recall–classify condition below the classify condition. A separation of the activity by response time showed greatest activity in DLPFC and greatest suppression of activity in the hippocampus for the memory task trials with the longest RTs. These experiments demonstrate that hippocampal activity is dissociated from prefrontal activity during a retrieval task requiring postretrieval processing; reduced activity in the hippocampus is distinct from the default-network MTL activity defined by comparing active versus passive baseline tasks.

Dissociation of Frontal and Hippocampal Activity

The results of these studies showed that DLPFC was most active and the hippocampus was least active during the recall–classify task. In imaging studies, DLPFC has been linked with numerous mnemonic and non-mnemonic functions, including LTM retrieval (Lundstrom et al., 2003; Wager & Smith, 2003; Ranganath, Johnson, & D'Esposito, 2000; Nolde, Johnson, & D'Esposito, 1998; Wagner, Desmond, Glover, & Gabrieli, 1998, Nyberg et al., 1995), maintenance and manipulation of items in WM (Cabeza & Nyberg, 2000), decision-making (Fleck et al., 2006), set shifting (Zanolie et al., 2008), and task difficulty (Braver et al., 1997; Manoach et al., 1997). Perhaps most relevant to the present study are its role in search processes subserving memory retrieval and its role in WM (see D'Esposito, 2007 for a review). DLPFC areas are activated when more information needs to be stored in WM (Rypma, Berger, & D'Esposito, 2002; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999; Braver et al., 1997; Smith & Jonides, 1997). The recall–classify task had components of recollection that would engage search processes, and postretrieval processing that would engage WM to hold the retrieved

Table 3. Clusters Significant ($p < .001$) for Even/Odd Discrimination versus Fixation Conditions

|	Talairach				
	x	*y*	*z*	*Volume*	*t*
(A) Even/Odd > Fixation					
L. Inferior parietal lobule (BA 40)	−44.1	−32.9	43.1	1536	8.33
R. Fusiform (BA 19)	38.1	−66.6	−6.4	768	6.21
L. Medial frontal gyrus (BA 6)	−6.8	−1.9	50.7	576	6.39
R. Declive	2	−56.5	−14.2	512	6.45
L. Inferior occipital gyrus (BA 18)	−32.8	−82.2	−2.2	448	5.25
R. Middle occipital gyrus (BA 18)	27.6	−87.2	−1.6	448	6.98
L. Thalamus	−13.2	−17.4	11.5	320	5.45
L. Inferior parietal lobule (BA 40)	−31.2	−49.5	40.8	320	6.45
L. Postcentral gyrus (BA 2)	−48.6	−29.8	52.5	320	6.41
(B) Fixation > Even/Odd					
R. Precuneus (BA 7)	3.6	−33.9	44.4	2688	−8.35
L. Posterior cingulate gyrus (BA 31)	−9.1	−38.6	38	960	−6.94
R. Subgyral (BA 40)	22.5	−36.1	56.6	960	−5.79
L. Cuneus (BA 7)	−11.5	−72.5	32.3	832	−8.50
L. Middle frontal gyrus (BA 46)	−40.1	43	3.5	448	−5.89
R. Parahippocampal gyrus (BA 36)	23.1	−39.3	−3.7	448	−7.71
L. Middle temporal gyrus (BA 39)	−48.2	−63.2	27.2	384	−7.24
R. Precuneus (BA 7)	16.5	−75.4	39.6	384	−6.90
L. Precuneus (BA 19)	−22.4	−77.3	41	384	−6.56
L. Inferior frontal gyrus (BA 45)	−46	38.3	1.4	320	−7.27
L. Precuneus (BA 31)	−7.4	−48.4	28	320	−4.80
R. Parahippocampal gyrus (BA 27)	24	−31.4	−8	256	−6.00
R. Insula (BA 13)	39.9	−23.1	16	256	−6.22
R. Posterior cingulate gyrus (BA 30)	9.2	−52.3	17.8	256	−5.61
R. Cuneus (BA 18)	8	−75.1	28	256	−4.92
L. Angular gyrus (BA 39)	−44.1	−67.4	36	256	−5.88

BA = Brodmann's area.
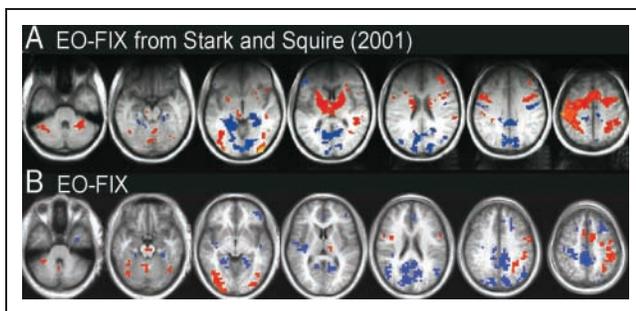
Figure 4. Experiment 1: Default-network activation. (A) Activation for the even/odd fixation condition modified from Stark and Squire (2001). (B) Activation for the even/odd fixation condition in the block-design study. Clusters with greater activation in the even/odd condition are shown in red and clusters with greater activation in the fixation condition are shown in blue. (Figure 4A reprinted with consent from the *Proceedings of the National Academy of Sciences, U.S.A.*, 2001).

Figure 5. Experiment 1: Activation in recall–classify versus classify and even/odd versus fixation contrasts. Top row: cut through the anterior hippocampus; bottom row: cut through the posterior parahippocampus for contrasts A, recall–classify versus classify and B, even/odd versus fixation. BOLD activation for clusters significant in each condition at $p < .01$. RC = recall–classify; C = classify; EO = even/odd discrimination; FIX = fixation. Interior clusters up to 9 mm deep are projected onto the surface and color scale bar represents percent signal change.

information in mind so classification could be performed. Thus, the dissociation of DLPFC and hippocampal activity observed during the recall–classify condition might have been enhanced by engagement of search processes before LTM retrieval, WM following LTM retrieval, or both. Following search and correct retrieval of an item from LTM, the hippocampal network might be suppressed as WM systems come on-line to work with the information retrieved. Such suppression may play a role in minimizing memory intrusion during postretrieval processing.

Direct connections between prefrontal cortex and MTL have been established through anatomical studies of the
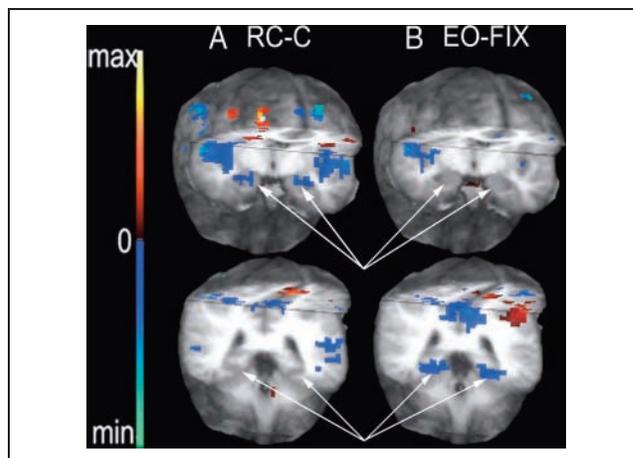
primate brain (Goldman-Rakic, Selemon, & Schwartz, 1984), and these connections have been examined non-invasively in humans using directional diffusion-weighted neuroimaging (Takahashi, Ohki, & Kim, 2007). Such findings provide a neuroanatomic basis for previous evidence of top–down modulation of MTL activity by prefrontal cortex (Gazzaley, Cooney, Rissman, & D'Esposito, 2005;
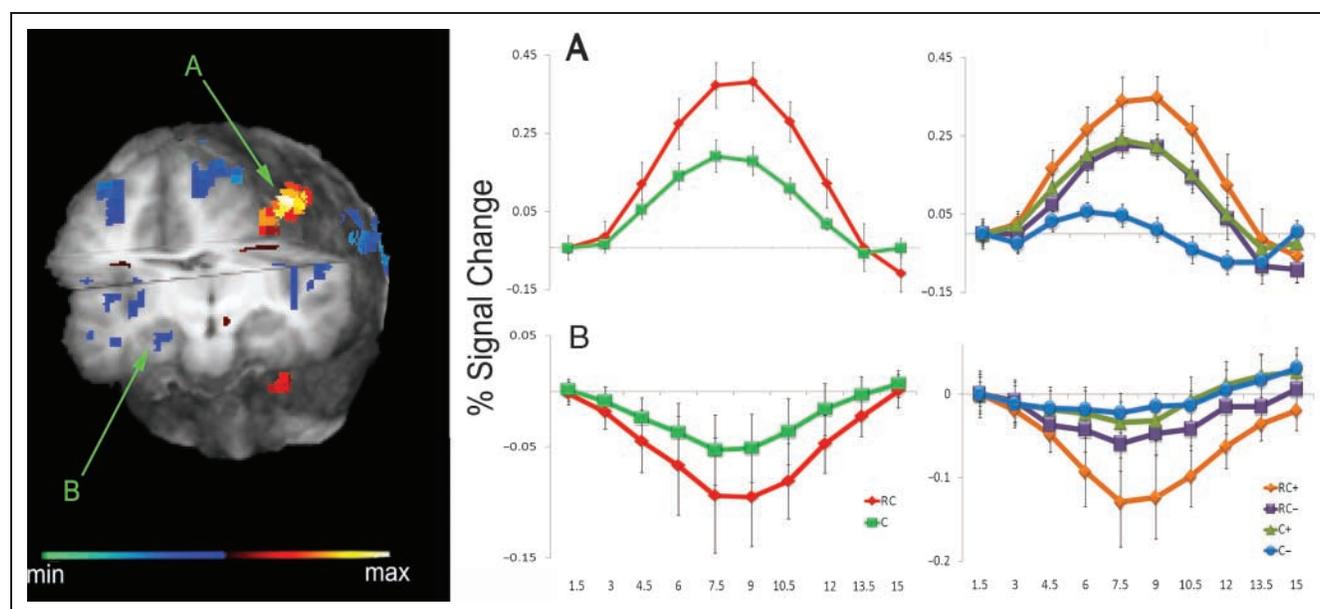

Figure 6. Experiment 2: Event-related DLPFC and hippocampal activation. Impulse–response curves for A, left DLPFC (−45, 15, 34), and B, right hippocampus (21, −15, −15) for recall–classify and classify conditions (left), separated into trials with a reaction time 1–3 *SD*s above (+) or below (−) the mean (right). Error bars represent *SEM*. Clusters used to extract impulse–response curves were from the recall–classify versus classify contrast at $p < .05$, shown on the image. RC = recall–classify; C = classify. Interior clusters up to 9 mm deep are projected into the surface and the color scale bar represent percent signal change.

Takahashi, Ohki, & Miyashita, 2002; Buckner, Koutstaal, Schacter, Dale, et al., 1998; Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998). The inversely correlated activity in prefrontal and MTL regions observed in the present study suggests that these two regions exhibit a dissociable functional response. Directed study of temporally linked prefrontal–MTL interaction will provide further information regarding the functional linkage between these regions.

Increases and Decreases in Hippocampal Activity Associated with Memory Retrieval

Prior studies have shown increases in hippocampal activity both during memory encoding (Uncapher & Rugg, 2005; Davachi et al., 2003; Fernandez et al., 1999; Lepage, Habib, & Tulving, 1998; Stern et al., 1996) and retrieval (Henson, 2005 for a review; Kahn, Davachi, & Wagner, 2004; Weis et al., 2004; Dobbins et al., 2003; Greicius et al., 2003; Ranganath & Rainer, 2003; Rugg, Henson, & Robb, 2003; Zeineh et al., 2003; Eldridge et al., 2000; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Dolan & Fletcher, 1997; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Schacter et al., 1995). A meta-analysis of PET studies found greater activation in the rostral portions of the hippocampus for encoding and greater activation in the caudal portions of the hippocampus for retrieval (Lepage et al., 1998). In each of these PET and fMRI studies, the subjects were shown an image or word and asked if they recognized it as previously seen or were cued to remember a word. The tasks employed in these studies did not require holding the retrieved item in mind for further processing. The clearest distinction between the tasks in the prior studies and those used in the current study is that the current recall–classify task demanded search, retrieval, and working with the item retrieved and did not rely solely upon recognition or cued recall.

The current findings are relevant to the interpretation of hippocampal activity differences during memory retrieval. Many studies have examined "old" versus "new" item contrasts at recognition and have reported greater hippocampal activity for confidently identified items (Daselaar, Fleck, & Cabeza, 2006; Slotnick & Schacter, 2004; Brewer & Gabrieli, 1997; Gabrieli et al., 1997). One potential confound is task difficulty. For certain task designs, judging an item as "old" may require less effort and less search than judging an item as "new." Similarly, studies have reported greater hippocampal activity for "remember" judgments (or items retrieved with high confidence) relative to "know" judgments (or items retrieved with low confidence) (Wixted & Stretch, 2004; Eldridge et al., 2000; Hockley & Consoli, 1999). Low-confidence retrieval might require more search and effort than high-confidence retrieval and, in light of the current findings, would be expected to lead to decreased hippocampal activity. In fact, examination of the parameter estimates reported by Yonelinas, Otten,

Shaw, and Rugg (2005) found that the hippocampus showed essentially no response for items judged as "remember," but negative parameter estimates for items judged as "familiar." In addition, a number of regions showing a similar decreased response for familiar judgments have been identified as default-network regions (ventromedial frontal and posterior cingulate). An additional consideration arises for such imaging studies that employ a retrieval task that includes a subsequent judgment of memory strength. The postretrieval processing required for subjects to assess and report memory strength may, itself, influence frontal and hippocampal activity. The neural bases of the judgments themselves and the differential influence of memory strength upon them remain unknown and have yet to be addressed through experimentation.

Memory Retrieval and the Default Network

In studies of recognition, the network of regions activated during episodic memory retrieval has been shown to overlap with the network of regions defined as the default network (Vincent et al., 2006; Buckner et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004). The hippocampus and adjacent MTL regions are known to be part of the default network (Greicius et al., 2004), and seeding hippocampus in a functional connectivity analysis reveals connectivity with the precuneus, posterior cingulate, and ventromedial frontal lobe, which are regions commonly identified as default network (Vincent et al., 2006). Although suppression of the default network has been attributed to many different cognitive functions, in this study, we observe deactivation of the default network, including the anterior hippocampus, during a difficult episodic recall task requiring postretrieval processing. Although this task might be expected to activate the retrieval network/default network, the opposite was seen. This suggests that task difficulty may be a more important modulator of this network than memory retrieval or internal focus of attention.

In Experiment 2, a trend toward hippocampal deactivation was seen during simple classification, which was not seen in the block-design experiment. It is possible that during the fixation task following a classify trial, inadvertent pair retrieval and processing occurred because all items had been studied as paired associates. This could explain the difference between the results obtained using a block design (where there was little time to further consider the stimuli before the next trial) and an event-related design with fixation (where there may have been time during fixation to further consider the preceding stimulus).

The MTL regions suppressed by the EO task differed from those suppressed by the recall–classify task, although both tasks led to suppression of non-MTL default regions. This suggests that the task employed may influence which components of the default network are modulated. In a review of default-network literature, Buckner, Andrews-Hanna, and Schacter (2008) discuss the default network

in terms of a core set of regions with high region-to-region correlations. MTL regions, including the parahippocampus and the hippocampus, comprise a subnetwork with variable correlation with other regions in the default network. Regions such as posterior cingulate/retrosplenial cortex and ventromedial prefrontal cortex show high correlation with the MTL subnetwork, whereas dorsomedial prefrontal cortex shows negative correlation with the MTL subnetwork. These findings suggest that the default network is not consistently activated as a unit, but rather that subcomponents may be more or less activated at different times. The present findings support such a notion. For example, the convergent findings between the present study and those of Stark and Squire (2001) would suggest that even/odd task performance results in suppression of posterior parahippocampal regions, performance of the recall–classify task results in suppression of the anterior hippocampus, and performance of the classify task does not result in significant suppression of MTL regions. Each of these tasks, however, does result in suppression of the core set of default regions—posterior cingulate/retrosplenial cortex and ventromedial prefrontal cortex.

Task Difficulty and the Default Network

Event-related fMRI allows examination of trial to trial differences in RT, which may provide insight into the relationships between frontal lobe activation, default-network suppression, MTL suppression, and task difficulty. Task difficulty could encompass the more specific interference of recall–classify trials where the categorization of the recalled image is different from that of the presented image, requiring avoidance of probe-induced interference. Alternatively, task difficulty could be related to memory strength, resulting in longer RTs for items poorly encoded. RT is often used as a marker of task difficulty and it has been employed to examine difficulty in categorization of items (Taylor & Thoroughman, 2008; Rajah, Ames, & D'Esposito, 2007; West & Holcomb, 2002; Demb et al., 1995; Kounios & Holcomb, 1994). In the present study when activation was examined in relation to RT, differing levels of activation in DLPFC and in the anterior hippocampus were observed. As seen in prior studies, DLPFC activity was highly related to RT, with longer RT associated with greater DLPFC activity in the recall–classify and classify conditions. Interestingly, anterior hippocampal activity showed the reverse pattern, where longer RTs were associated with more suppressed hippocampal activity in the recall–classify condition only. Thus, in DLPFC it is possible that the activity difference is due to classification difficulty, whereas in the hippocampus it would appear that there is an interaction between recollection and task difficulty.

Conclusion

The present study demonstrates that DLPFC and hippocampal activity are dissociated during difficult episodic retrieval tasks and that the default network/hippocampus is suppressed during episodic memory retrieval and post-retrieval processing. Default-network regions outside the MTL were suppressed by all tasks relative to passive fixation, but the anterior hippocampus was suppressed only during episodic retrieval with postretrieval processing. These findings were replicated and extended in a second group of subjects demonstrating greater dissociation of DLPFC and hippocampal activity in memory recall trials with longer RTs. These studies demonstrate that DLPFC and hippocampal regions, often diverging when default network is activated, also may diverge during episodic retrieval. This suggests a more complex relationship during retrieval and postretrieval processing. Exploring difficulty of memory retrieval judgments in relation to the default network could shed light on memory recall studies showing an overlap of the retrieval and default networks. Directed study of the divergence in frontal and hippocampal activity related to search, retrieval, and post-retrieval processing may help identify the role of cooperation and competition between memory systems in everyday function.

REFERENCES

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., et al. (2004). Neural systems underlying the suppression of unwanted memories. *Science, 303,* 232–235.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of precortex involvement in human working memory. *Neuroimage, 5,* 49–62.

Brewer, J. B., & Gabrieli, J. D. (1997). Focusing in on the medial temporal lobe. *Molecular Psychiatry, 2,* 430–431.

Brewer, J. B., & Moghekar, A. (2002). Imaging the medial temporal lobe: Exploring new dimensions. *Trends in Cognitive Sciences, 6,* 217–223.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science, 281,* 1185–1187.

Buckner, R. L. (2003). Functional–anatomic correlates of control processes in memory. *Journal of Neuroscience, 23,* 3999–4004.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124,* 1–38.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Dale, A. M., Rotte, M., & Rosen, B. R. (1998). Functional–anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. *Neuroimage, 7,* 163–175.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D., & Rosen, B. R. (1998). Functional–anatomic study of episodic retrieval using fMRI: I. Retrieval effort versus retrieval success. *Neuroimage, 7,* 151–162.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., et al. (2005). Molecular, structural, and functional characterization of Alzheimer's Disease: Evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience, 25,* 7709–7717.

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: Default activity and spontaneous network correlations. *Neuroimage, 37,* 1097–1099.

Cabeza, R., & Nyberg, L. (2000). Neural bases of learning and memory: Functional neuroimaging evidence. *Current Opinion in Neurology, 13,* 415–421.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29,* 162–173.

Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: Recollection, familiarity, and novelty. *Journal of Neurophysiology, 96,* 1902–1911.

Daselaar, S. M., Rice, H. J., Greenberg, D. L., Cabeza, R., LaBar, K. S., & Rubin, D. C. (2008). The spatiotemporal dynamics of autobiographical memory: Neural correlates of recall, emotional intensity, and reliving. *Cerebral Cortex, 18,* 217–229.

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: Distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences, U.S.A., 100,* 2157–2162.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience, 15,* 5870–5878.

Depue, B. E., Curran, T., & Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science, 317,* 215–219.

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 362,* 761–772.

Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: Separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41,* 318–333.

Dolan, R. J., & Fletcher, P. C. (1997). Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature, 388,* 582–585.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience, 3,* 1149–1152.

Esposito, F., Bertolio, A., Scarabino, T., Latorre, V., Blasi, G., Popolizio, T., et al. (2006). Independent component model of the default-mode brain function: Assessing the impact of active thinking. *Brain Research Bulletin, 70,* 263–269.

Fernandez, G., Effern, A., Grunwald, T., Pezer, N., Lehnertz, K., Dumpelmann, M., et al. (1999). Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science, 285,* 1582–1585.

Fleck, M. S., Daselaar, S. M., Dobbins, I. G., & Cabeza, R. (2006). Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and nonmemory tasks. *Cerebral Cortex, 16,* 1623–1630.

Fransson, P. (2006). How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia, 44,* 2836–2845.

Gabrieli, J. D., Brewer, J. B., Desmond, J. E., & Glover, G. H. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science, 276,* 264–266.

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top–down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience, 8,* 1298–1300.

Goldman-Rakic, P. S., Selemon, L. D., & Schwartz, M. L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience, 12,* 719–743.

Greicius, M. D., Krasnow, B., Boyett-Anderson, J. M., Eliez, S., Schatzberg, A. F., Reiss, A. L., et al. (2003). Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. *Hippocampus, 13,* 164–174.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences, U.S.A., 101,* 4637–4642.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences, U.S.A., 98,* 4259–4264.

Heekeren, H. R., Marrett, S., Bandettini, P. A., & Ungerleider, L. G. (2004). A general mechanism for perceptual decision-making in the human brain. *Nature, 431,* 859–862.

Henson, R. N. (2005). A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. *Quarterly Journal of Experimental Psychology: B, Comparative and Physiological Psychology, 58,* 340–360.

Henson, R. N., Rugg, M. D., Shallice, T., & Dolan, R. J. (2000). Confidence in recognition memory for words: Dissociating right prefrontal roles in episodic retrieval. *Journal of Cognitive Neuroscience, 12,* 913–923.

Hockley, W. E., & Consoli, A. (1999). Familiarity and recollection in item and associative recognition. *Memory & Cognition, 27,* 657–664.

Kahn, I., Davachi, L., & Wagner, A. D. (2004). Functional–neuroanatomic correlates of recollection: Implications for models of recognition memory. *Journal of Neuroscience, 24,* 4172–4180.

Kapur, S., Craik, F. I., Jones, C., Brown, G. M., Houle, S., & Tulving, E. (1995). Functional role of the prefrontal cortex in retrieval memories: A PET study. *NeuroReport, 6,* 1880–1884.

Kounios, J., & Holcomb, P. J. (1994). Concreteness effects in semantic processing: ERP evidence supporting dual-coding theory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 804–823.

Lepage, M., Habib, R., & Tulving, E. (1998). Hippocampal PET activations of memory encoding and retrieval: The HIPER model. *Hippocampus, 8,* 313–322.

Lundstrom, B. N., Petersson, K. M., Andersson, J., Johansson, M., Fransson, P., & Ingvar, M. (2003). Isolating the retrieval

of imagined pictures during episodic memory: Activation of the left precuneus and left prefrontal cortex. *Neuroimage, 20,* 1934–1943.

Manoach, D. S., Schlaug, G., Siewert, B., Darby, D. G., Bly, B. M., Benfield, A., et al. (1997). Prefrontal cortex fMRI signal changes are correlated with working memory load. *NeuroReport, 8,* 545–549.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science, 315,* 393–395.

McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., & Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience, 15,* 394–408.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 4,* 257–267.

Nolde, S. F., Johnson, M. K., & D'Esposito, M. (1998). Left prefrontal activation during episodic remembering: An event-related fMRI study. *NeuroReport, 9,* 3509–3514.

Nyberg, L., McIntosh, A. R., Houle, S., Nilsson, L. G., & Tulving, E. (1996). Activation of medial temporal structures during episodic memory retrieval. *Nature, 380,* 715–717.

Nyberg, L., Tulving, E., Habib, R., Nilsson, L. G., Kapur, S., Houle, S., et al. (1995). Functional brain maps of retrieval mode and recovery of episodic information. *NeuroReport, 7,* 249–252.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, U.S.A., 98,* 676–682.

Rajah, M. N., Ames, B., & D'Esposito, M. D. (2007). Prefrontal contributions to domain-general executive control processes during temporal context retrieval. *Neuropsychologia, 46,* 1088–1103.

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *Journal of Neuroscience, 20,* RC108.

Ranganath, C., & Rainer, G. (2003). Neural mechanisms for detecting and remembering novel events. *Nature Reviews Neuroscience, 4,* 193–202.

Rossion, B., & Pourtois, G. (2004). Revisiting Snodgrass and Vanderwart's object pictorial set: The role of surface detail in basic-level object recognition. *Perception, 33,* 217–236.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1996). Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain, 119,* 2073–2083.

Rugg, M. D., Henson, R. N., & Robb, W. G. (2003). Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. *Neuropsychologia, 41,* 40–52.

Rugg, M. D., & Wilding, E. L. (2000). Retrieval processing and episodic memory. *Trends in Cognitive Sciences, 4,* 108–115.

Rypma, B., Berger, J. S., & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience, 14,* 721–731.

Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage, 9,* 216–226.

Schacter, D. L., Reiman, E., Uecker, A., Polster, M. R., Yun, L. S., & Cooper, L. A. (1995). Brain regions associated with retrieval of structurally coherent visual information. *Nature, 376,* 587–590.

Slotnick, S. D., & Schacter, D. L. (2004). A sensory signature that distinguishes true from false memories. *Nature Neuroscience, 7,* 664–672.

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology, 33,* 5–42.

Stark, C. E., & Squire, L. R. (2001). When zero is not zero: The problem of ambiguous baseline conditions in fMRI. *Proceedings of the National Academy of Sciences, U.S.A., 98,* 12760–12766.

Stern, C. E., Corkin, S., Gonzalez, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., et al. (1996). The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences, U.S.A., 93,* 8660–8665.

Takahashi, E., Ohki, K., & Kim, D. S. (2007). Diffusion tensor studies dissociated two fronto-temporal pathways in the human memory system. *Neuroimage, 34,* 827–838.

Takahashi, E., Ohki, K., & Miyashita, Y. (2002). The role of the parahippocampal gyrus in source memory for external and internal events. *NeuroReport, 13,* 1951–1956.

Talairach, J., & Tournoux, P. (1998). *A co-planar stereotaxic atlas of the human brain.* Stuttgard: Thieme.

Taylor, J. A., & Thoroughman, K. A. (2008). Motor adaptation scaled by the difficulty of a secondary cognitive task. *PLoS One, 3,* 1–11.

Uncapher, M. R., & Rugg, M. D. (2005). Encoding and the durability of episodic memory: A functional magnetic resonance imaging study. *Journal of Neuroscience, 25,* 7260–7267.

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., et al. (2006). Coherent spontaneous activity identifies a hippocampal–parietal memory network. *Journal of Neurophysiology, 96,* 3517–3531.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective, and Behavioral Neuroscience, 3,* 255–274.

Wagner, A. D., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. *Brain, 121,* 1985–2002.

Wagner, A. D., Maril, A., Bjork, R. A., & Schacter, D. L. (2001). Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage, 14,* 1337–1347.

Weis, S., Specht, K., Klaver, P., Tendolkar, I., Willmes, K., Ruhlmann, J., et al. (2004). Process dissociation between contextual retrieval and item recognition. *NeuroReport, 15,* 2729–2733.

West, W. C., & Holcomb, P. J. (2002). Event-related potentials during discourse-level semantic integration of complex pictures. *Brain Research, Cognitive Brain Research, 13,* 363–375.

Wixted, J. T., & Stretch, V. (2004). In defense of the signal detection interpretation of remember/know judgments. *Psychonomic Bulletin & Review, 154,* 103–114.

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *Journal of Neuroscience, 25,* 3002–3008.

Zanolie, K., Teng, S., Donohue, S. E., van Duijvenvoorde, A. C., Band, G. P., Rombouts, S. A., et al. (2008). Switching between colors and shapes on the basis of positive and negative feedback: An fMRI and EEG study on feedback-based learning. *Cortex, 44,* 537–547.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face–name pairs. *Science, 299,* 577–580.