Prefrontal and hippocampal contributions to visual associative recognition: Interactions between cognitive control and episodic retrieval

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Abstract

The ability to recover episodic associations is thought to depend on medial–temporal lobe mnemonic mechanisms and frontal lobe cognitive control processes. The present study examined the neural circuitry underlying non-verbal associative retrieval, and considered the consequences of successful retrieval on cognitive control demands. Event-related fMRI data were acquired while subjects retrieved strongly or weakly associated pairs of novel visual patterns in a two-alternative forced choice associative recognition paradigm. Behaviorally, successful retrieval of strongly associated relative to weakly associated pairs was more likely to be accompanied by conscious recollection of the pair’s prior co-occurrence. At the neural level, right ventrolateral prefrontal cortex (VLPFC) and hippocampus were more active during successful retrieval of Strong than of Weak associations, consistent with a role in visual associative recollection. By contrast, Weak trials elicited greater activation in right anterior cingulate cortex (ACC), which may detect conflict between the similarly familiar target and foil stimuli in the absence of recollection. Consistent with this interpretation, stronger ACC activity was associated with weaker hippocampal and stronger right dorsolateral PFC (DLPFC) responses. Thus, recollection of relevant visual associations (hippocampus and VLPFC) results in lower levels of mnemonic conflict (ACC) and decreased familiarity-based monitoring demands (DLPFC). These findings highlight the interplay between cognitive control and episodic retrieval.

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1. Introduction

One challenge we regularly face is that of retrieving specific knowledge associated with a stimulus. Numerous studies in humans and other animals have clearly demonstrated the importance of the hippocampus in forming and retrieving episodic associations (Brasted, Bussey, Murray, & Wise, 2003; Cohen & Eichenbaum, 1993; Corkin, 2002; Gabrieli, 1998; Squire, 1992; see also O’Reilly & Rudy, 2001). Recent evidence indicates that hippocampal mechanisms may be particularly important for the ability to consciously recollect prior experiences (e.g., Baddeley, Vargha-Khadem, & Mishkin, 2001; Brown & Aggleton, 2001; Davaechi, Mitchell, & Wagner, 2003; Dobbins, Foley, Schacter, & Wagner, 2002; Eldridge, Knowlton, Furmanski, Bookheimer, &
Engel, 2000; Holdstock et al., 2002; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001; Yonelinas et al., 2002; but see Stark, Bayley, & Squire, 2002; Manns, Hopkins, Reed, Kitchener, & Squire, 2003). Beyond the hippocampus, neuropsychological and neuroimaging findings suggest that prefrontal cortex (PFC) contributes to retrieval, perhaps by playing a role in guiding or controlling knowledge recovery (e.g., Buckner, Raichle, Miezin, & Petersen, 1996; Incisa della Rocchetta & Milner, 1993; Janowsky, Shimamura, & Squire, 1989; Kapur et al., 1995; Moscovitch & Melo, 1997; Petrides, Alivassatos, & Evans, 1995; Rugg & Wilding, 2000; Schacter, 1997; Stallion et al., 1994; Shimamura, 1995; Wagner, Desmond, Glover, & Gabrieli, 1998a). For example, ventrolateral PFC (VLPFC) is thought to subserve mechanisms that support both the formation and controlled retrieval of associations between representations (e.g., Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Passingham, Toni, & Rushworth, 2000; Petrides, 2002; Petrides et al., 1995; Wagner, Pare-Blagoef, Clark, & Poldrack, 2001), whereas right dorsolateral PFC (DLPFC) may mediate the monitoring of stimulus familiarity (e.g., Dobbins, Rice, Wagner, & Schacter, 2003; Henson, Rugg, Shallice, & Dolan, 2000; Henson, Shallice, & Dolan, 1999a). Although it is generally accepted that hippocampal mnemonic mechanisms and PFC cognitive control processes contribute to episodic retrieval, the neural substrates of visual-associative retrieval and the potential interplay between these mnemonic and cognitive control processes remain poorly understood.

Few brain imaging studies have examined visual associative recognition in humans; moreover, to our knowledge, extant studies have focused primarily on the role of the medial temporal lobes (Henke, Buck, Weber, & Wieser, 1997; Klingberg, Roland, & Kawashima, 1994; Stark & Squire, 2001a). These studies have shown that activation of the hippocampus and/or surrounding cortex is greater for retrieval of associative than non-associative information (Klingberg et al., 1994), with activation particularly marking successful retrieval (Stark & Squire, 2001a).

Complementary electrophysiological and lesion data from non-human primates provide additional clues regarding the neural circuitry underlying retrieval of visual associations. Such studies have implicated inferotemporal and medial temporal cortices in the long-term storage of visual associations (Miyashita, 1988; Murray, Gaffan, & Mishkin, 1993; Sakai & Miyashita, 1991), and have demonstrated that top-down inputs from prefrontal cortex to temporal regions are critical for retrieving these associations (Eacott & Gaffan, 1989; Hasegawa, Fukushima, Ihara, & Miyashita, 1998; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999; see Miyashita & Hayashi, 2000). Furthermore, lesion studies have implicated one PFC subregion in particular—VLPFC—in learning and retrieving associations between stimuli or between a stimulus and a response (Passingham et al., 2000).

In humans, left anterior VLPFC has been implicated in the retrieval of semantic associations (Badre & Wagner, 2002; Buckner, Raichle, & Peterson, 1995; Fiez, 1997; Gabrieli, Poldrack, & Desmond, 1998; Gabrieli et al., 1996; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Poldrack et al., 1999). This region is particularly modulated by controlled retrieval demands, exhibiting greater activation during retrieval of weak than of strong pre-experimental semantic associations (Bunge, Badre, & Wagner, in press; Wagner et al., 2001). Left anterior VLPFC is also recruited during the retrieval of novel word-word associations (Mottaghy et al., 1999).

Whereas left VLPFC has been associated with semantic associative retrieval, one possibility is that multiple VLPFC subregions guide retrieval depending on the target knowledge domain. Domain-sensitivity has been observed during episodic encoding and item retrieval—words vs. faces (Kelley et al., 1998; McDermott, Buckner, Petersen, Kelley, & Sanders, 1999), words vs. visual textures (Wagner et al., 1998b), and words vs. visual scenes (Kirchhoff, Wagner, Maril, & Stern, 2000; for review see Buckner, Kelley, & Petersen, 1999; Wagner, Koutstaal, & Schacter, 1999). These studies suggest that left VLPFC is preferentially engaged during the controlled processing of verbal-semantic stimuli, whereas right VLPFC is preferentially engaged during the processing of visual-object (non-verbal) stimuli. Evidence that controlled retrieval is a common function of VLPFC subregions would come from the finding that VLPFC associative strength effects generalize to other forms of knowledge (e.g., visual) and to novel (i.e., experimentally-derived) associations. In the present experiment, we sought to determine whether engagement of right VLPFC during associative recognition is modulated by the strength of novel associations between visual stimuli that lack meaning and that are difficult to name.

The role of PFC in cognitive control and retrieval is not restricted to VLPFC. For example, activation in right DLPFC is commonly observed in studies of episodic retrieval (Fletcher & Henson, 2001; Henson, Rugg, Shallice, Josephs, & Dolan, 1999). One hypothesis is that right DLPFC mechanisms may serve to monitor retrieved information to determine its veracity or task-relevance (Henson et al., 1999b, 2000). In particular, right DLPFC activation tends to be greater under situations that require monitoring of, and decisions based on, the relative familiarity of stimuli (Dobbins et al., 2003; Eldridge et al., 2000; Henson et al., 1999a, 1999b), being differentially engaged when making decisions that are near criterion (Henson et al., 2000). These results suggest that demands on DLPFC monitoring
and response selection mechanisms should be high when subjects are unable to select between competing memoranda on the basis of episodic recollection, and thus are forced to consider the relative familiarity of choice stimuli.

In the present experiment, subjects intentionally learned novel associations between pairs of visual patterns. The strength of the formed associations was manipulated by varying the number of times that two patterns were paired together during learning (11 times on Strong trials and 4 times on Weak trials), while holding constant the total number of times (12) that each pattern was presented at study. We then acquired event-related fMRI data while subjects performed an associative recognition task. On each trial of the retrieval test, subjects had to decide which of two patterns had been associated with a cue pattern at study. The foil pattern (i.e., the incorrect choice) was highly familiar, having also been studied 12 times, but was irrelevant because it had never been paired with the cue pattern. Of central interest was the effect of varying associative strength (Strong vs. Weak) on the neural correlates of successful visual associative recognition. In addition to the fMRI study, we conducted a companion behavioral study to assess the extent to which successful associative recognition decisions on Strong and Weak trials were accompanied by conscious recollection. These behavioral data proved informative in guiding interpretation of the observed fMRI retrieval responses.

We predicted that the hippocampus and right VLPFC would be important for successful retrieval of visual associations, and therefore would be modulated by the strength of the newly formed associations. We further expected that, in the absence of associative recollection, mnemonic conflict would be present during recognition attempts because the target and foil stimuli were both designed to be highly familiar. Accordingly, in the absence of recollection and in the face of conflicting familiarity signals, subjects may come to rely more heavily on cognitive control processes that monitor for subtle differences in item or associative familiarity. As numerous studies have suggested that the anterior cingulate cortex (ACC) may detect conflict, we anticipated that this region would be differentially engaged during associative retrieval trials that lack recollection. Moreover, given the putative role of right DLPFC in monitoring stimulus familiarity, we anticipated that this region would be differentially engaged during situations of high mnemonic conflict (i.e., robust ACC engagement) that arise due to low recollection (i.e., weak hippocampal engagement). Thus, we predicted a negative relation between hippocampal/VLPFC mechanisms that support recollection of visual associations and ACC/DLPFC control mechanisms that detect conflict and aim to resolve this conflict by monitoring for differential familiarity.

2. Materials and methods

2.1. Subjects

Fourteen right-handed native English-speaking volunteers (7 females; ages 19–34 years, \( M = 24 \)) were included in the study. Three additional subjects were excluded on the basis of technical difficulties, and six additional subjects were excluded on the basis of poor task performance (recognition accuracy lower than 60% in one or more conditions). Informed consent was obtained in a manner approved by the Committee on the Use of Humans as Experimental Subjects at MIT, and the Institutional Review Board of the Massachusetts General Hospital. Subjects received $50 remuneration for their participation.

2.2. Study session

During a 1-h study session, subjects viewed a series of colored patterns on a computer screen. Stimuli were presented for 1400 ms, with an inter-trial interval of 100 ms. Each of 210 patterns was presented alone and/or paired with a specific pattern (Fig. 1). Subjects were instructed to memorize which patterns were paired together, and informed that they would later be tested on their memory for the pattern pairs. Each of 35 pattern pairs were presented 11 times at study (Strong association condition), with the members of each pair also being initially presented alone 1 time (thus totalling 12 presentations of each pattern). Each of 35 other pattern pairs were presented 4 times (Weak association condition), with the members of each pair also being initially presented alone 8 times (thus totalling 12 presentations for each pattern). An additional 70 patterns were presented alone 12 times; these stimuli served as foils in the later forced-choice
associative recognition memory test. Inclusion of the foils in the study phase ensured that subsequent associative recognition could not be based simply on large differences in item familiarity (see below).

The study session consisted of six phases separated by short breaks. Each phase contained a fixed number of single and paired presentations of each stimulus, and trials were pseudorandomly ordered within a phase. Study lists were counterbalanced across subjects, such that stimuli that were designated as Strong for half of the subjects were designated as Weak for the other half.

2.3. Test session

FMRI data were acquired while subjects performed a two-alternative forced-choice associative recognition test. On each trial, a set of three patterns—a cue that appeared above a target and a foil—was presented for 4 s (Fig. 1). Subjects were instructed to press one of two buttons under their left hand to indicate which of the choice stimuli had been paired with the cue during study. Subjects performed a total of 70 test trials over the course of a 7-min scan, 35 of which tested recognition of newly-formed, Strong visual associations and 35 of which tested recognition of newly-formed, Weak visual associations. Periods of visual fixation lasting between 2 and 8 s, jittered in increments of 2 s, were interspersed between trials as determined by a design optimization algorithm (Dale, 1999).

2.4. Behavioral study: Assessing associative recollection

Because the fMRI test phase only required subjects to indicate which of the two choice stimuli had been paired with the cue at study, evidence regarding the mnemonic basis for each decision was limited. To determine the degree to which correct associative recognition decisions were based on conscious recollection, we conducted a follow-up behavioral experiment with a separate group of subjects. During the test phase of this experiment, subjects were asked to indicate whether each recognition decision was based on associative recollection (‘Remember’), associative or differential item familiarity (‘Know’), or guessing (‘Guess’) (Conway, Gardiner, Perfect, Anderson, & Cohen, 1997; Tulving, 1985). Collection of these behavioral data was designed to determine whether the probability of recollection-based versus familiarity-based associative recognition was higher during Strong than during Weak trials.

During the behavioral experiment, participants were 11 right-handed native English-speaking volunteers (7 females; ages 19–24 years; \( M = 21 \)). Data from 3 additional subjects were excluded because of poor performance. Subjects encountered an identical study session to that used in the fMRI experiment. Following a 30-min delay, which approximated the retention interval in the fMRI experiment, subjects performed a two-alternative forced-choice test. This test was identical to that performed by subjects in the scanner, with the additional requirement that, after making a recognition choice, they were asked to indicate the basis for this memory decision: ‘Remember’, ‘Know’, or ‘Guess’ (Conway et al., 1997). Subjects responded ‘Remember’ if they specifically remembered seeing the pair of patterns together at study, and were informed that such remembering might entail recollecting a image of the co-occurrence of the two patterns or some other detail about the study encounter. Subjects responded ‘Know’ when they were unable to recall a specific episode when the patterns were paired together but nevertheless felt that they knew the correct answer. Finally, subjects responded ‘Guess’ when their recognition choice was a guess, rather than being based on remembering or knowing. Subjects indicated their response by pressing one of three keys.

2.5. FMRI data acquisition

Visual stimuli were projected onto a screen that was viewed through a mirror. Scanning was performed on a 1.5T Siemens system using a standard whole-head coil. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2 s, TE = 40 ms, 21 axial slices, 3.125 \( \times \) 3.125 \( \times \) 5 mm, 1 mm inter-slice gap, 210 volumes). During the functional scan, the first four volumes were discarded to allow for T1-equilibration effects. High-resolution T1-weighted (MP-RAGE) anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head.

Data were preprocessed using SPM99 (Wellcome Dept. of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction (using sinc interpolation). Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a non-linear transformation involving cosine basis functions, and resampled the volumes to 3-mm cubic voxels. Templates were based on the MNI305 stereotactic space (Cocosco, Kollokian, Kwan, & Evans, 1997), an approximation of Talairach space (Talairach & Tourneaux, 1988). Functional volumes were spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.
Statistical analyses were performed using the general linear model in SPM99. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. The resulting functions were used as covariates in a general linear model, along with a basis set of cosine functions that high-pass filtered the data. Head motion parameters (estimates of $x$, $y$, and $z$ translation and rotation over the course of the scan) were included in the analysis as covariates of no interest. The least squares parameter estimates of height of the best fitting synthetic HRF for each condition were used in pairwise contrasts, and the resulting contrast images computed on a subject-by-subject basis were submitted to group analyses. Incorrect recognition trials were modeled separately from correct trials, and were not included in the statistical analyses.

At the group level, contrasts between conditions were computed by performing one-tailed $t$ tests on the contrast images, treating subjects as a random effect. Unless otherwise noted, we used a standard statistical threshold adopted in numerous prior event-related fMRI studies (5 or more contiguous voxels exceeding an uncorrected threshold of $p < .001$). In addition, following others (e.g., Davachi & Wagner, 2002; Dobbins et al., 2003; Eldridge et al., 2000; Strange, Fletcher, Henson, Friston, & Dolan, 1999), we adopted the slightly more lenient threshold of $p < .005$ (5 voxel extent) for the medial temporal lobe (MTL), given the lower signal-to-noise ratio often observed in MTL regions (Ojemann et al., 1997; Schacter & Wagner, 1999). Finally, given the limited power of the present study design—data were collected in a single 7-min scan, with 35 Strong and 35 Weak trials—we additionally report effects in the a priori expected ACC region that exceeded this more lenient threshold. Performance issues required adoption of this moderately-powered design, because behavioral piloting indicated that 35 trials per condition was the maximum number of pattern pairs that subjects could learn in a single study session.

Region-of-interest (ROI) analyses were performed to further characterize the response profiles of brain regions identified from the group analyses. ROIs included all significant voxels within a 6-mm radius of each maximum. Signal within an ROI was calculated for each subject by selectively averaging the data with respect to peristimulus time for trials in each condition. Statistics were performed on the peak percent signal change, which occurred at a peristimulus time of 6 s in all ROIs. Additionally, regions whose activation was correlated with ACC activation were identified by a between-subjects regression analysis. The Weak > fixation contrast image for each subject was submitted to this group analysis, together with a linear regressor consisting of each subject’s average peak percent signal change in ACC on Weak trials. As detailed in the Introduction, the motivation for this regression analysis was to determine whether ACC conflict monitoring mechanisms were negatively correlated with hippocampal recollective processes, and positively correlated with DLPFC familiarity-monitoring processes.

3. Results

3.1. Associative recognition performance

As predicted, additional learning with the paired patterns during study was associated with enhanced associative recognition at test (Fig. 2A). Specifically, subjects in the fMRI experiment were more accurate
(t(13) = 5.2; p < .0002) and responded more quickly (t(13) = 7.4; p < .0001) on Strong than on Weak trials. Similarly, subjects in the supplementary behavioral study were more accurate (.93 and .76 correct, respectively; t(10) = 6.4; p < .0001) and responded more quickly (1942 and 2313 ms; t(10) = 6.1; p < .0002) on Strong than on Weak trials.

3.2. Mnemonic basis for associative recognition: Assessing differential recollection

The objective of the behavioral experiment was to determine whether correct recognition was differentially based on recollection during Strong relative to Weak trials. A repeated-measures ANOVA on correct trials, with factors of Associative strength (Strong, Weak) and Memory (proportion of Remember, Know and Guess responses), revealed a significant interaction (F(2,20) = 29.6; p < .0001; Fig. 2B). Post-hoc tests revealed that the proportion of correct recognition decisions accompanied by a Remember judgment was higher for Strong than for Weak trials (F(1,10) = 50.4; p < .0001). The proportion of Know judgments did not differ between the two trial types (F < 1), whereas Guessing was more prevalent on Weak than on Strong trials (F(1,10) = 12.1; p < .003). Importantly, few Strong or Weak trials resulted in an incorrect response accompanied by a Remember or Know judgment, indicating that, although the basis for correct memory decisions differed between Strong and Weak trials, nevertheless these correct decisions primarily reflected true memory (rather than guessing).

3.3. Neural correlates of visual associative recollection

The supplementary behavioral study suggests that correctly recognized Strong trials were largely based on successful recollection of the visual associations, whereas recognized Weak trials were less likely to be accompanied by recollection. Thus, to identify regions associated with successful recollection, we examined the effect of Associative strength (correct Strong > correct Weak). This contrast identified an anterior region in right VLPFC (~BA 47; Fig. 3A), as well as regions in right visual association cortex (middle occipital cortex; ~BA 18), right superior frontal cortex (~BA 8), left medial frontal cortex (~BA 10), and left precentral cortex (~BA 4; Table 1). Moreover, and importantly, activation was also observed in right anterior hippocampus (p < .005; Fig. 3B). These data indicate that right VLPFC and hippocampus, in conjunction with occipito-temporal cortices, are differentially engaged when associative recognition is more likely to be based on conscious recollection, suggesting that these structures contribute to or are modulated by the recollection of visual associative knowledge.

### Table 1

<table>
<thead>
<tr>
<th>Region modulated by associative strength</th>
<th>MNI coordinates</th>
</tr>
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<tbody>
<tr>
<td>Strong &gt; Weak</td>
<td>~BA x  y  z  Z score</td>
</tr>
<tr>
<td>Inferior frontal cortex</td>
<td>R47 45 39 15 3.39</td>
</tr>
<tr>
<td>Medial frontal cortex</td>
<td>L10 12 51 3 3.48</td>
</tr>
<tr>
<td>Precentral cortex</td>
<td>L4 21 12 27 3.66</td>
</tr>
<tr>
<td>Superior frontal cortex</td>
<td>R8 21 36 54 4.18</td>
</tr>
<tr>
<td>Middle occipital cortex</td>
<td>R18 24 12 12 4.27</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>R 27 12 15 3.18</td>
</tr>
<tr>
<td>Weak &gt; Strong</td>
<td>~BA x  y  z  Z score</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>R32 12 18 39 3.60</td>
</tr>
</tbody>
</table>

~BA = approximate Brodmann’s area.

* A priori region of interest identified at p < .005 (uncorrected). A full list of coordinates at p < .005 is available upon request.

3.4. Left VLPFC and visual associative retrieval

To determine whether the left VLPFC region previously implicated in controlled semantic retrieval also contributes to the retrieval of novel visual associations that differ in associative strength, we applied an ROI derived from Wagner et al. (2001; focus centered on ~BA 21–12) to the present dataset. This region, which has been shown to be sensitive to pre-experimental semantic associative strength (more active during Weak versus Strong trials), was insensitive to the strength of the newly-learned, visual associations investigated here (t(1,13) = .48; p = .64). Moreover, in the present study, a slightly more anterior region in left VLPFC (BA 47; ~BA 47) was engaged by performance of our visual associative recognition task (Strong + Weak trials > fixation). An ROI analysis focusing on left BA 47 revealed that this region was only marginally more active on Strong than Weak trials (t(13) = 1.88; p = .08). Thus, in contrast to right VLPFC, there was limited evidence that left VLPFC subserves retrieval of visual associations. Nonetheless, although effects of associative strength were significant in right but not left VLPFC, strong conclusions about lateralization are not possible because ANOVAs with within-subject factors of laterality and associative strength failed to demonstrate a laterality × associative strength effect for either of the two left VLPFC ROIs relative to right VLPFC (Fs < 1).

3.5. Neural correlates of mnemonic conflict and familiarity monitoring

Because the probability of basing a correct recognition decision on recollection was lower on Weak trials, the comparison of Weak to Strong trials serves to identify regions that are engaged when associative recognition decisions require discrimination between two choice stimuli that are both familiar but lack recollection. Accordingly, we expected that Weak trials would be differentially asso-
associated with greater mnemonic conflict due to having to adjudicate between two familiar choice stimuli without recourse to recollection to guide the recognition decision. Although the comparison of Weak to Strong trials failed to yield significant activations at the standard statistical threshold, differential activation was observed in ACC at the more liberal threshold adopted for a priori expected regions ($p < .005$; Fig. 4A).

ACC activity appears to mark the presence of familiarity-based conflict between the target and foil, in the absence of recollection. To the extent that this is the case, one would expect a negative correlation between ACC activation and activation in regions thought to subserve recollection (i.e., hippocampus); that is, recollection should reduce conflict. In addition, one also would expect a positive correlation between ACC activation and activation in regions thought to be engaged when subjects must monitor levels of familiarity as a basis for recognition decisions (e.g., right DLPFC; Dobkins et al., 2003; Henson et al., 1999b, 2000).

Both predictions were borne out by a between-subjects whole-brain regression analysis identifying regions in which the magnitude of activation on Weak trials was correlated with the level of ACC activation on Weak trials. Specifically, activation in right DLPFC (middle/inferior frontal cortex; ~BA 46) was positively correlated with that in ACC on Weak trials ($p < .001$; Fig. 4B). Right DLPFC was also positively correlated with ACC activity on Strong trials ($R^2 = .54; p < .003$).

In contrast to the positive correlation observed between ACC and right DLPFC, a negative correlation was observed between ACC and left anterior hippocampus on Weak trials ($p < .005$; Fig. 4C). A subsequent ROI analysis did not obtain evidence for a correlation between left hippocampus and ACC on Strong trials ($R^2 = .004$). However, when Strong and Weak trials were included together in the SPM regression analysis, a negative correlation was observed between ACC and left hippocampus at a more liberal threshold ($p < .0075$), suggesting that the two regions may have been correlated across conditions. ROI analysis further revealed that the left anterior hippocampus was more active on Strong than Weak trials ($t(13) = 2.18; p < .05$), similar to the pattern observed in right anterior hippocampus in the group contrast of Strong > Weak trials. As with its left-sided counterpart, activation in the right hippocampal ROI appeared to have a negative relationship with ACC activation. However, the correlation was only significant when the subject with the highest ACC activation was excluded from the analysis ($R^2 = .44; p < .02$). Collectively these

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2 The correlations of left hippocampus and right DLPFC with ACC remained reliable (both $ps < .01$) upon exclusion of this subject.
data implicate bilateral anterior hippocampus in visual associative recollection, and suggest that greater hippocampal recruitment was associated with lower ACC activation.

4. Discussion

The present study sought to identify the neural correlates of episodic retrieval of novel associations between visual stimuli, and to examine interactions between mnemonic and cognitive control processes. To this end, we manipulated the strength of association (Strong vs. Weak) between pairs of colored patterns. Behaviorally, subjects were more accurate and faster during retrieval of pairs that had co-occurred a greater number of times at study (Strong trials). Moreover, a supplementary behavioral experiment requiring Remember/Know/Guess judgments indicated that correctly recognized Strong trials were differentially associated with recollection (Remember judgements) than were correct Weak trials. These behavioral findings suggest that brain regions differentially activated by Strong than Weak trials—which included right anterior hippocampus and right VLPFC—may subserve or be modulated by successful recollection of visual associative knowledge. In contrast, regions differentially activated by Weak relative to Strong trials—notably the ACC—likely reflect the greater conflict between competing mnemonic (familiarity-based) representations in the absence of recollection. Moreover, greater conflict (ACC activation) was associated with increased monitoring demands (DLPFC activation). Thus, under certain situations, the ability to recollect the past can result in reduced demands on certain forms of cognitive control.

4.1. Hippocampus

Right and, to a lesser extent left, anterior hippocampus was more active at retrieval for strongly than weakly associated pattern pairs. This finding is consistent with numerous studies emphasizing the role of hippocampus in relational or conjunctive processing (Cohen & Eichenbaum, 1993; Davachi & Wagner, 2002; Eichenbaum, 2000; O’Reilly & Rudy, 2001; Squire, 1994; Stark & Squire, 2001a). Extant data suggest that hippocampus binds the various features of an event into an integrated memory trace at encoding, and that at retrieval hippocampal mechanisms interact with neocortical representations to reinstantiate the features associated with the stimulus that cues remembering. Consistent with this view, recent event-related fMRI studies of episodic retrieval have demonstrated that hippocampal activation is greatest under conditions in which subjects successfully recollect the context or other experiential details associated with an item’s prior encounter (Dobbins et al., 2003; Eldridge et al., 2000; Yonelinas et al., 2001).

Particularly relevant to the present study, Eldridge et al. (2000) observed greater bilateral hippocampal activation during word recognition accompanied by ‘Remembering’ than by ‘Knowing’, with the latter condition not differing from correct rejections. Moreover, Dobbins et al. (2002) observed that hippocampal activation differentiated between successful and unsuccessful source recollection, but did not discriminate between successful and unsuccessful recognition when these decisions were based on assessing differential stimulus familiarity. Moreover, it has been suggested that anterior hippocampus is preferentially engaged under conditions that encourage relational processing of two or more stimuli (Dolan & Fletcher, 1997; Henke et al., 1997; for reviews see Lepage, Habib, & Tulving, 1998; Schacter & Wagner, 1999). The present hippocampal findings build on this literature, which to date has focused primarily on verbal-semantic associations, by demonstrating greater anterior hippocampal activation during retrieval conditions that are differentially accompanied by recollection of recently learned visual associations.

4.2. VLPFC

As predicted, visual associative retrieval engaged not only the hippocampus but also right VLPFC. The region in right VLPFC (~BA 47; pars orbitalis) observed to be differentially activated by retrieval of Strong relative to Weak pattern associations is similar to a region implicated in recognizing previously studied patterns (Cadoret, Pike, & Petrides, 2001; Petrides, Alivisatos, & Frey, 2002) or faces (Kostopoulos & Petrides, 2003; although it falls anterior and ventral to that observed in the pattern recognition study of Wagner et al., 1998b). The present data extend previous findings by suggesting that, above and beyond subserving recognition of individual visual objects, right VLPFC is engaged when retrieving associations between multiple visual objects. The involvement of BA 47 in memory for visual associations is consistent with neuroanatomical evidence indicating that the likely homologue in non-human primates receives strong inputs from visual association areas (Pandya & Yeterian, 1996; Petrides & Pandya, 2001). Furthermore, the present results are consistent with a growing literature suggesting that VLPFC activation is domain-sensitive, with right VLPFC preferentially engaged by visuo-object information (Hazeltine, Bunge, Scanlon, Rosen, & Gabrieli, 2003; Kelley et al., 1998; Kirchhoff et al., 2000; Klingberg & Roland, 1998; McDermott et al., 1999; Wagner, 2002; Wagner et al., 1998b).

It may be worth noting that the right VLPFC responses during both Strong and Weak trials fell below baseline. At present, the functional significance of
task-induced deactivation relative to a resting baseline is not yet fully understood. One interpretation is that such response patterns reflect the interruption of ongoing cognitive operations that occur at rest, such as visual imagery and memory recall (Binder et al., 1999; Gussnard & Raichle, 2001; Mazoyer et al., 2001; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Shulman et al., 1997; Stark & Squire, 2001b). Nevertheless, focusing on the relative difference between activation on Strong and Weak trials, the present results provide new evidence that activity in right VLPFC across trials correlates with the level of successful recollection of non-verbal associative knowledge.

Left anterior VLPFC, which has been implicated in retrieving semantic associations (for reviews, see Badre & Wagner, 2002; Poldrack et al., 1999), does not appear to be as important as right anterior VLPFC for retrieving visual associations. One region in left VLPFC (BA 47; −48 33 −12) was quantitatively more active on Strong than on Weak trials, but this effect was not statistically reliable. This region appears to be anatomically similar to that observed in several studies of semantic associative retrieval (Wagner et al., 2001: −48 33 −12; Bunge et al., in press: −48 30 9). However, those studies observed the opposite pattern to that observed here in left VLPFC, as well as in right VLPFC, namely greater activation during the retrieval of weaker than of stronger associations.

At present it is unclear why the present study revealed greater activation in right VLPFC during retrieval of strong relative to weak visual associations, whereas prior studies have observed less activation in left VLPFC during retrieval of strong relative to weak semantic associations. One possibility is that VLPFC mechanisms are particularly recruited when subjects engage retrieval processes that lead to the successful recollection of knowledge, be it episodic recollection of visual associations or semantic recollection of the conceptual relations between stimuli, with these mechanisms being recruited when recollection is effortful (Wagner et al., 2001). However, under situations in which initial recollection attempts are unsuccessful and participants shift to relying on an assessment of stimulus familiarity, one might then observe diminished reliance on VLPFC processes (see also Dobbins et al., 2003). According to this account, one should observe greatest activation in VLPFC during effortful or controlled recollection, intermediate levels during less effortful or more automatic recollection, and the least activation during conditions encouraging familiarity monitoring. The present results are consistent with the hypothesis that VLPFC is important for active mnemonic retrieval under situations in which relevant associations do not readily spring to mind—i.e., when relations between representations are weak, unstable, or ambiguous (Petrides, 2002; see also Miller & Cohen, 2001).

4.3. ACC and DLPFC

In contrast to VLPFC and hippocampus, right ACC was more active on Weak than Strong trials. Moreover, the strongest ACC signal was obtained for subjects who exhibited the weakest activation in hippocampus. The ACC focus identified here is close to a focus exhibiting greater activation when word recognition decisions are accompanied by ‘Knowing’ relative to ‘Remembering’ (Eldridge et al., 2000; see also Maril, Wagner, & Schacter, 2001). These convergent findings suggest that this subregion within ACC is differentially engaged under retrieval conditions in which recollection levels are poor.

More generally, the present ACC focus also falls in the vicinity of ACC activations observed during the performance of tasks that have been characterized as involving conflict between multiple representations (e.g., Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Carter et al., 2000; for review see van Veen & Carter, 2002). ACC (specifically, the rostral cingulate zone) has been hypothesized to detect the presence of conflict between competing response representations (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter, Botvinick, & Cohen, 1999; Carter et al., 1998), and it has been argued that the role of ACC in conflict detection may generalize to other types of representations (van Veen & Carter, 2002). The ACC signal in the present study is likely related to the need to select between two familiar patterns at test. In the absence of reliable recollection (i.e., on Weak trials), the foil pattern serves as an effective distractor because it is highly familiar yet irrelevant, never having been paired with the cue pattern. Accordingly, in the absence of recollection, mnemonic conflict between competing familiarity signals is present and may be detected by ACC monitoring mechanisms.

The conflict theory holds that ACC-generated signals modulate cognitive control processes subserved by DLPFC—processes that may in turn resolve the conflict by selectively enhancing the activity of task-relevant representations in cortical association areas (Braver, Cohen, & Barch, 2002; Cohen, Braver, & O’Reilly, 1996; MacDonald, Cohen, Stenger, & Carter, 2000; Miller & Cohen, 2001) or by monitoring for subtle differences in stimulus familiarity (Dobbins et al., 2003; Henson et al., 2000; Henson et al., 1999b). Consistent with previous findings that ACC and DLPFC functionally interact (Gehring & Knight, 2000), we observed that subjects who recruited right ACC more strongly during retrieval also tended to recruit right DLPFC more strongly. As noted previously, right DLPFC activation in memory retrieval studies has been interpreted as reflecting post-retrieval monitoring demands, which may be greater when subjects fail to recollect contextual details of an item’s study encounter (Henson et al., 1999b; Schacter,
1997; Wagner et al., 1998a; for review see Fletcher & Henson, 2001). Supporting this view are data showing greater activation in right DLPFC during recognition accompanied by ‘Knowing’ relative to ‘Remembering’ (Henson et al., 1999a), recognition associated with low relative to high confidence (Henson et al., 2000), and recognition based on assessments of relative recency rather than source recollection (Dobbins et al., 2003). In the context of the present study, a greater conflict signal from ACC, due to lower levels of recollection (i.e., weaker hippocampal signals), may lead to greater familiarity-based monitoring in an effort to select between the similarly familiar target and foil stimuli.

The present results support the view that greater conflict detection during attempts to remember the past is associated with greater allocation of specific forms of cognitive control. As such, the present data highlight the interplay between mnemonic mechanisms and cognitive control processes. Accordingly, it appears that our ability to remember the past is an emergent product of interacting hippocampal and prefrontal processes, some of which support recovery of experiential details whereas others support attempts to work with memory in the absence of recollection.

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