Domain-general and Domain-sensitive Prefrontal Mechanisms for Recollecting Events and Detecting Novelty

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Recollecting the past and discriminating novel from familiar memoranda depend on poorly understood prefrontal cortical (PFC) mechanisms hypothesized to vary according to memory task (e.g. recollection versus novelty detection) and domain of targeted memories (e.g. perceptual versus conceptual). Using event-related fMRI, we demonstrate that recollecting conceptual or perceptual details surrounding object encounters similarly recruits left frontopolar and posterior PFC compared with detecting novel stimuli, suggesting that a domain-general control network is engaged during contextual remembering. In contrast, left anterior ventrolateral PFC coactivated with a left middle temporal region associated with semantic representation, and right ventrolateral PFC with bilateral occipito-temporal cortices associated with representing object form, depending on whether recollections were conceptual or perceptual. These PFC/posterior cortical dissociations suggest that during recollection, lateralized ventrolateral PFC mechanisms bias posterior conceptual or perceptual feature representations as a function of memory relevance, potentially improving the gain of bottom-up memory signals. Supporting this domain-sensitive biasing hypothesis, novelty detection also recruited right ventrolateral PFC and bilateral occipito-temporal cortices compared with conceptual recollection, suggesting that searching for novel objects heavily relies upon perceptual feature processing. Collectively, these data isolate task- from domain-sensitive PFC control processes strategically recruited in the service of episodic memory.

Keywords: attention, cognitive control, familiarity, fMRI, memory, prefrontal cortex

Introduction

Memory permits an organism to distinguish previously encountered (familiar) from novel stimuli, and to consciously recollect specific details surrounding a prior stimulus encounter (Mandler, 1980; Tulving, 1985; Jacoby, 1991; Yonelinas, 2002). For example, when bumping into a colleague, we depend on memory to signal whether or not the individual is familiar, and if so, to consciously recollect details about the prior encounter (e.g. remembering conceptual details of a past discussion or perceptual details about the person's prior appearance). Prefrontal cortical (PFC) mechanisms are critical for judgements that require recollection (e.g. source memory decisions) (Milner, 1982; Petrides and Milner, 1982; Smith and Milner, 1984; Janowsky et al., 1989; Shimamura et al., 1991; Johnson et al., 1993; Incisa della Rocchetta and Milner, 1993; Moscovitch and Melo, 1997; Nolde et al., 1998; Schacter et al., 1998; Rugg et al., 1999; Ranganath et al., 2000; Raye et al., 2000; Dobbins et al., 2002), although the contributions of the various subregions of PFC to memory retrieval remain poorly understood. To gain leverage on PFC function at retrieval, the present experiment addressed two fundamental questions:

(i) Are the PFC mechanisms engaged during recollection sensitive to the domain (e.g. conceptual versus perceptual) of the to-be-recollected information, or are they recruited during recollection irrespective of the nature of the sought-after details? (ii) What is the relation between the PFC mechanisms that guide recollection and those that guide discrimination of novel from familiar stimuli?

Cognitive models of remembering suggest that recollection partially depends on several interdependent control processes that support (i) specification or refinement of retrieval plans; (ii) elaboration on memory probes in the service of retrieval plans; and (iii) evaluation and selection of recovered episodic content with respect to decision criteria (Raaijmakers and Shiffrin, 1981; Rugg and Wilding, 2000; Fletcher and Henson, 2001; Kahn et al., 2004). Furthermore, initial neuroimaging data suggest that anatomically separable PFC subregions may differentially contribute to each of these component processes of recollection. For example, Dobbins et al. (2002) implicated left frontopolar and posterior dorsolateral PFC in the monitoring or evaluative stage of recollection, whereas left anterior ventrolateral PFC appeared to contribute to the semantic elaboration of retrieval probes. Importantly, in this prior study, the criterial knowledge to be recollected was conceptual, raising the possibility that some left PFC contributions to recollection are specific to the conceptual domain. However, because Dobbins et al. (2002) did not systematically contrast recollection of conceptual versus perceptual event details, uncertainty remains regarding the domain-specificity or conversely the domain-generality of these left PFC contributions to recollection.

Domain-generality of PFC-mediated retrieval processes is suggested (though not necessitated) by the finding that, across experiments targeting perceptual and conceptual recollection (Ranganath et al., 2000; Dobbins et al., 2002; Buckner, 2003), left frontopolar cortex [~Brodmann's area (BA) 10] is activated to a greater extent during the contextual recollection condition (i.e. source memory) versus conditions likely related to item familiarity or novelty assessments (Nolde et al., 1998; Rugg et al., 1999; Ranganath et al., 2000; Raye et al., 2000; Dobbins et al., 2002). Moreover, a subregion of left ventrolateral PFC (~BA 45/44) has been hypothesized to guide retrieval whenever subjects must select task-relevant information from amongst mutually competing irrelevant mnemonic representations, regardless of the domain of those representations (Thompson-Schill et al., 1997; Buckner, 2002, 2003; Gold and Buckner, 2002). From this perspective, the prominence of left ventrolateral PFC activity during source recollection compared with item recognition paradigms results because the former requires selection of one of multiple competing contextual details about a past encounter, whereas item familiarity/novelty decisions

can be made without reference to the specifics of the prior encounters and hence do not require selecting from among particular contextual details (Buckner, 2002; Velanova *et al.*, 2003).

In contrast to domain-general interpretations of left PFC activity during source recollection, based on evidence implicating left anterior ventrolateral PFC (~BA 47/45) in controlled semantic processing (Fiez, 1997; Poldrack *et al.*, 1999; Wagner *et al.*, 2001b) and evidence for lateralized ventrolateral PFC responses during episodic encoding and retrieval depending on stimulus content (Kelley *et al.*, 1998; Wagner *et al.*, 1998), Dobbins *et al.* (2002) hypothesized that left anterior ventrolateral PFC is engaged during conceptual recollection because this region supports processes that enable conceptual elaboration of retrieval probes. According to this conceptual elaboration hypothesis, left anterior ventrolateral PFC underlies attention to or retrieval of those conceptual attributes of the recognition probe that are most closely related to the desired episodic information. Because episodic retrieval is probe dependent (Anderson and Bower, 1973; Raaijmakers and Shiffrin, 1981), conceptual elaboration improves the probe's efficiency by biasing representations that are from the same conceptual neighborhood as the to-be-recollected content, thus increasing the likelihood of triggering recollection of the desired detail(s). This proposed biasing mechanism is consistent with operations envisioned within the source monitoring framework, in which subjects are assumed to flexibly weight different features during remembering, depending upon their belief about the types of recovered information that will be most diagnostic for identifying a particular origin of a memory (e.g. Johnson *et al.*, 1993).

Importantly, whereas left PFC has been implicated in recollection-based retrieval, initial neuroimaging studies have given rise to different hypotheses regarding the role of right PFC structures during retrieval. For example, motivated by dual-process theories of recognition, right PFC activity has been interpreted as a marker of familiarity monitoring (Henson *et al.*, 1999, 2000; Dobbins *et al.*, 2003, 2004). Under this account, monitoring of a continuous or scalar familiarity signal in relation to an internal decision criterion, similar to that proposed in signal detection theory and global matching models of recognition (Banks, 1970; Hintzman, 1984), is thought to recruit right dorsolateral and frontopolar PFC regions. An alternate perspective posits that right PFC processes, particularly ventrolateral mechanisms, are engaged during retrieval when attention must be oriented to visuo-perceptual representations (Wagner *et al.*, 1998; Wagner, 1999). This latter mechanism can be thought of as the complement to that supporting conceptual probe elaboration, wherein subjects selectively attend to or retrieve relevant visuo-perceptual attributes of the recognition probe during retrieval attempt. To the extent that left and right ventrolateral PFC direct attention towards — or bias processing in — different representational domains, then it should be possible to dissociate these subregions during recollection by steering retrieval towards conceptual or perceptual aspects of the past, even while holding the memory probes constant. Moreover, one might expect to see a consequence of this domain-sensitive biasing in posterior cortical brain structures that are known to differentially represent conceptual or perceptual knowledge.

To isolate domain-general and domain-sensitive PFC processes that contribute to recollection, we developed two source retrieval tasks that held retrieval probes and selection demands constant while varying the type of probe elaboration likely to be recruited during attempts to recollect (conceptual versus perceptual). Specifically, the domain-sensitivity of PFC responses was directly examined by contrasting different source memory judgements on matched pictorial stimuli; one source task targeted recovery of perceptual details about past experiences with the probes (perceptual source), whereas the other targeted recovery of conceptual aspects of prior processing of those objects (conceptual source) (Fig. 1). Critically, any observed neural differences between these source recollection conditions should reflect PFC control mechanisms that are sensitive to the domain of the to-be-recollected information because the history and form of the retrieval probes was identical across cuing conditions.

Both source tasks were further compared with a novelty detection task that required assessment of relative stimulus familiarity, with minimal recollection demands (Fig. 1). Thus, novelty detection served as a reference condition for the two source tasks, permitting identification of regions that are similarly and increasingly engaged during any attempt to recollect particular experiential details irrespective of the nature of those details (i.e. domain-general processes). Finally, inclusion of the novelty detection condition also allowed for assessment of whether the mechanisms engaged during familiarity-based recognition bear any relation to those supporting perceptual or conceptual recollection.

Materials and Methods

Subjects
Fourteen right-handed, native English speaking volunteers (five females; 18–35 years old) were paid $50 for participating. Three additional subjects were excluded from analysis, two due to poor performance and one to misinterpreting the instructions. Informed consent was obtained consistent with the institutional review boards at Massachusetts General Hospital and MIT.

Study Materials
Color pictures of 396 common, easily nameable objects were drawn from a previously described set (Simons *et al.*, 2003). Pictures were divided into two sets, used in two separate scanning runs. Within each run, the 198 pictures were further subdivided into six lists of 33 items, with lists being rotated through conditions across subjects. Four lists were used during study with the remaining two used as novel items during test. For each item, there were three screen versions: an 'intermediate' size; a 'small' size, which was a 50% scaled reduction of the intermediate; and a 'large' size, which was a 50% scaled increase of it (cf. Ranganath *et al.*, 2000).

Procedure
The experiment consisted of two cycles of Study 1, Study 2 and Test (Fig. 1). Each cycle began with a 5.5 min study phase (Study 1), during which subjects performed a (non-scanned) one-back perceptual size judgement task on 132 pictures (each presented for 2 s, randomly intermixed with 33 fixation events). Half of the pictures were presented in a large size and half in a small size; subjects indicated whether each was larger or smaller in screen area compared with the picture seen on the previous trial. Judgements were based on the screen size of the object, and not the real-world size of the referent; responses were made with a keypad. This study phase ensured that participants intentionally attended to the perceptual size of each object, increasing the likelihood that they would be able to recollect this perceptual dimension when required at retrieval.

During Study 2, subjects were scanned while making either a living/nonliving or pleasant/unpleasant semantic judgement about the same 132 pictures, each depicted in the identical size as in Study 1. During this 11 min scan, each 4 s trial began with a 100 ms blank screen

Study Phases
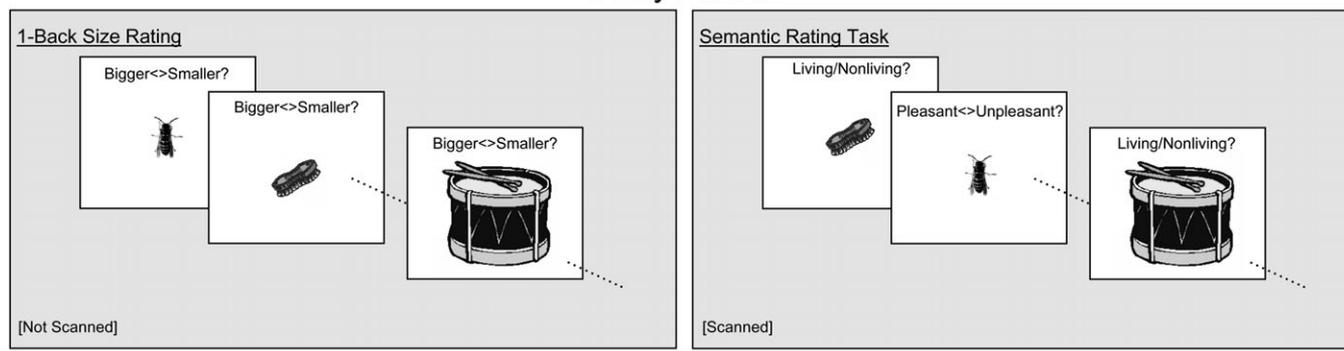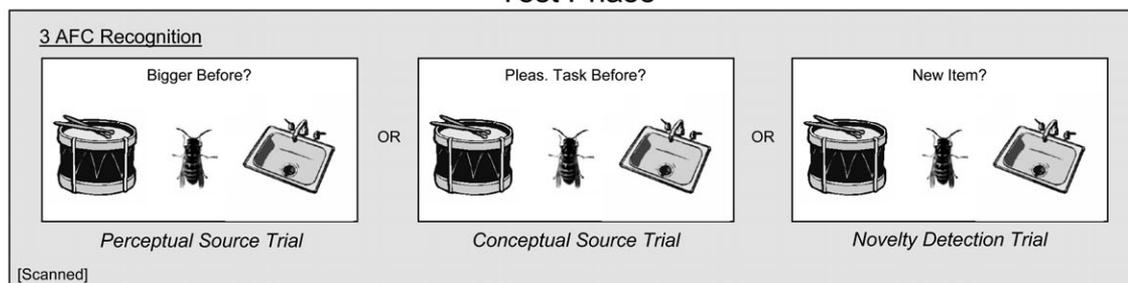
Figure 1. Experimental design. During the initial encounter, items were shown individually and subjects decided if each item occupied a bigger screen area than the immediately preceding item (one-back size rating). This manipulation was not scanned and was conducted in order to familiarize the subjects with the screen size of the objects. Immediately following, one of two semantic encoding judgements (pleasant/unpleasant or living/nonliving) was performed on pictures that maintained the same physical size as during the one-back task. At test, three objects were shown (one novel and two studied) in an intermediate and similar size, and either novelty detection or one of two source judgements was required (source versus novelty detection). Conceptual source retrieval required selection of the item earlier rated for pleasantness, whereas the perceptual source task required selecting the one that was physically larger on the screen during previous viewings.

followed by a 3500 ms task cue that appeared above the location of the upcoming stimulus. The picture appeared 100 ms after task cue onset, remaining centrally for 3000 ms; a 400 ms blank screen appeared at the end of the trial. Key presses were made with the left index and ring finger. Picture trials were intermixed with null events, consisting of a cross ('+') below the cue 'rest'. Conditions were pseudo-randomly ordered in a manner that optimized design efficiency (Wager and Nichols, 2003).

Immediately following Study 2, subjects were scanned while making episodic memory judgements. This 9.2 min test contained 92 trials, of which 26 were fixations. The remaining 66 trials required a memory judgement on triplets of pictures, all shown in an intermediate size. Test triplets contained two studied and one novel picture — one old item had been studied in a small size, the other in a large size; one had been encoded via the living/nonliving task, the other via the pleasant/unpleasant task. Study size (small or large) was crossed with the conceptual encoding task performed at Study 2 (living/nonliving or pleasant/unpleasant), ensuring that perceptual experiential details (i.e. size) and conceptual experiential details (i.e. encoding task) were uncorrelated. Of the 66 test trials, 14 required novelty-detection ('new-item?'), 26 required a conceptual source judgement ('pleas.-task-before?') and 26 required a perceptual source judgement ('bigger-before?'). The location of the correct item within the triplet was pseudo-randomized; again, trial order was determined by an optimal sequencing program (Wager and Nichols, 2003).

On each 6 s test trial, a 100 ms blank screen preceded onset of a 5300 ms task cue; the three pictures appeared 100 ms after cue onset (duration 5000 ms). Subjects responded while the pictures were on the screen using the index, middle and ring finger of the left hand, which corresponded to the screen location of the pictures (right, middle or left).

fMRI Data Acquisition

Imaging was performed on a 3 T Siemens Trio whole body scanner using a standard head coil. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2 s, TE = 30 ms, 21 axial slices parallel to the AC–PC plane, 3.125 × 3.125 × 5 mm with a 1 mm gap, interleaved collection). Four initial dummy volumes were discarded to allow for equilibration effects. A high-resolution T1-weighted (MP-RAGE) anatomical volume was collected. Head motion was restricted using a pillow and foam inserts.

fMRI Data Analysis

Preprocessing using SPM99 (Wellcome Department of Cognitive Neurology, London) included slice acquisition timing correction followed by rigid body motion correction. Functional data were normalized to an EPI template (MNI-152), with volumes then resampled into 3 mm cubes and spatially smoothed with an 8 mm FWHM Gaussian kernal. Each scanning session was rescaled to a mean signal whole volume intensity of 100 (proportional scaling).

Subjects were statistically treated as a random effect. Volumes were treated as a time series and modeled by convolving a canonical hemodynamic response function and its first-order time derivative using the onset times of the conditions of interest. The resulting functions were entered into a general linear model along with a basis set that was used to high-pass filter the data and a covariate representing session effects. The least squares parameter estimates of the height of the response for each contrast were stored as a separate image for each subject. For analyses investigating regional overlap across different contrasts, a region was considered reliable if it was activated at the $P < 0.0316$ level for each of two independent contrasts such that inclusive masking established a joint threshold of $P < 0.001$ for five or more contiguous voxels. For study–test comparisons, each contrast was necessarily independent since they were obtained in different phases of the experiment. When overlap comparisons were restricted to test-phase conditions, a separate test scan from each of the two cycles was used to construct each contrast image for each subject, again yielding two independent contrast images arising from separate scans. Finally, for tests involving only one pairwise contrast, regions were considered

reliable using the same threshold achieved in the inclusive masks (5 or more voxels that exceeded a threshold of $P < 0.001$). Thus for all reported contrasts, the nominal threshold is 0.001 (5 voxels), which is consistent with that employed in the majority of episodic memory investigations and allows meaningful across study comparisons.

Regions of interest (ROIs) were extracted, averaging from 0–20 s post-stimulus onset based on the canonical model. Percent signal time courses consisted of the average of the above-threshold voxels within an 8 mm radius of the SPM-identified maxima for the relevant contrasts. Graphical renderings were performed with MRIcro (http://www.psychology.nottingham.ac.uk-/staff/cr1/index.html).

Results

Behavioral Performance

Behavioral and fMRI analyses were restricted to correct trials. Reaction times differed across the three retrieval tasks [$F(2,26)$ = 16.12, $P < 0.001$], being similar during conceptual (2534 ms) and perceptual (2621 ms) source recollection ($P > 0.27$), both of which took longer than novelty detection (2202 ms; Ps < 0.001). Accuracy also differed across the retrieval tasks [$F(2,26)$ = 11.38, $P < 0.001$], being superior during novelty detection (0.94) relative to perceptual source recollection (0.88) and conceptual source recollection (0.84) ($P < 0.05$ and $P < 0.001$, respectively). Perceptual source recollection was more accurate than conceptual source recollection ($P < 0.05$), although the absolute magnitude of the difference was modest (4%). The overall similarity of source recollection accuracy during the perceptual and conceptual tasks likely partially stems from having had subjects intentionally orient once to object size and once to object meaning during study. Importantly, this similarity in recollection accuracy ensures that differences in neural activation across these conditions do not reflect global differences in effort or task difficulty.

fMRI Results

Event-related fMRI analyses identified whether distinct processes contributed to episodic recollection in a domain-general or a domain-sensitive manner, and assessed the relation between the processes guiding recollection and those supporting familiarity-based novelty detection. Accordingly, analyses indexed (i) neural responses that generalized across the two source recollection tasks relative to novelty detection (Table 1, Fig. 2a); and (ii) responses that were sensitive to the specific mnemonic domain (perceptual versus conceptual) targeted during source recollection (Tables 2 and 3, Fig. 2b,c). Regions demonstrating domain-sensitive recollection effects were further examined to assess their responses during novelty detection.

Neural Correlates of Domain-general Recollection

Inclusive masking of contrasts drawn from independent test scans revealed greater activity during both perceptual and conceptual source recollection compared with novelty detection in several left lateralized regions, including frontopolar (~BA 10) and dorsolateral PFC (~BAs 9/8/46), subregions within posterior ventrolateral PFC (~BAs 44 and 45) and inferior parietal cortex (~BA 40) (Table 1, Fig. 2a). This network of regions converges with that identified in a prior study comparing source recollection to novelty-detection using words (Dobbins *et al.*, 2002), thus demonstrating that the left lateralization often seen during source recollection is not simply due to the use of verbal materials (Ranganath *et al.*,

Table 1

Regions demonstrating domain-general activation during source recollection[a]

Region	MNI coordinates			Voxels	~BA
Prefrontal cortices					
L frontopolar (1)[b]	−36	54	3	33	10
L frontopolar/ventrolateral	−45	42	−15	13	10/47
L frontopolar	−33	51	−12	17	11/10
L frontopolar/dorsolateral	−45	48	12	9	10/46
L dorsolateral (2)	−39	21	48	34	8
L dorsolateral	−42	27	30	31	9/46
L dorsolateral	−33	30	51	16	8
L dorsolateral	−45	15	45	47	8
L dorsolateral	−42	9	51	51	6/8
L dorsolateral/frontopolar	−48	42	6	9	46/10
R dorsolateral	45	27	48	9	8/9
L posterior ventrolateral (3)	−51	18	6	23	44/45
L mid-ventrolateral	−51	24	15	33	45
L anterior ventrolateral	−54	24	−3	16	45/47
L anterior ventrolateral	−30	27	−12	5	47
L superior frontal	−6	12	60	8	6
L superior frontal	−3	21	66	11	6/8
L superior frontal	−3	21	54	25	8
L superior frontal	−6	33	48	39	8
L medial frontal/anterior cingulate	−6	36	33	27	8/32
L medial frontal	−6	45	42	13	8
L anterior cingulate	−12	30	27	12	32
Other regions					
L inferior parietal (4)	−42	−51	54	31	40
L inferior parietal	−48	−45	48	29	40
L supramarginal gyrus	−36	−54	33	21	40
L angular gyrus	−33	−63	33	19	39
L precuneus	−6	−69	48	19	7
precuneus	0	−69	42	18	7
R precuneus	12	−60	39	41	7
L inferior occipital	−12	−90	−12	5	17
L caudate	−12	15	−3	5	–

[a]Joint probability, $P < 0.001$: (conceptual source > novelty detection) + (perceptual source > novelty detection).
[b]Numerals inside parentheses denote regions of interest plotted in Figure 2a. ~BA = approximate Brodmann's area; L = left; R = right.

2000; Buckner, 2003). Critically, activation in these regions did not differ when the perceptual and conceptual source conditions were directly compared, even at a very liberal threshold ($P > 0.1$; Fig. 2a), providing new evidence that these structures support cognitive control and mnemonic processes that are engaged during attempts to recollect irrespective of the nature of the to-be-recollected experiential details.

Of these regions, the majority demonstrated minimal above-baseline activity during novelty detection suggesting that they are strategically recruited when recollection of specific experiential details is required (Fig. 2a; Dobbins *et al.*, 2002). An exception to this source-selective pattern was the response of posterior ventrolateral PFC (~BA 44/45), which also demonstrated strong activation during novelty detection relative to baseline (Fig. 2a, region 3). This finding is consistent with a hypothesized role of left posterior ventrolateral PFC in representing retrieval probes in working memory during both recollective and familiarity-based retrieval attempts (Dobbins *et al.*, 2002).

Neural Correlates of Domain-sensitive Recollection

Recollecting Conceptual Details

Regions differentially engaged during attempts to recollect conceptual, rather than perceptual, details were identified through regional overlap of a Study 2 contrast and a test-phase contrast, both of which highlighted heightened conceptual elaboration. The primary purpose of using this conjunction
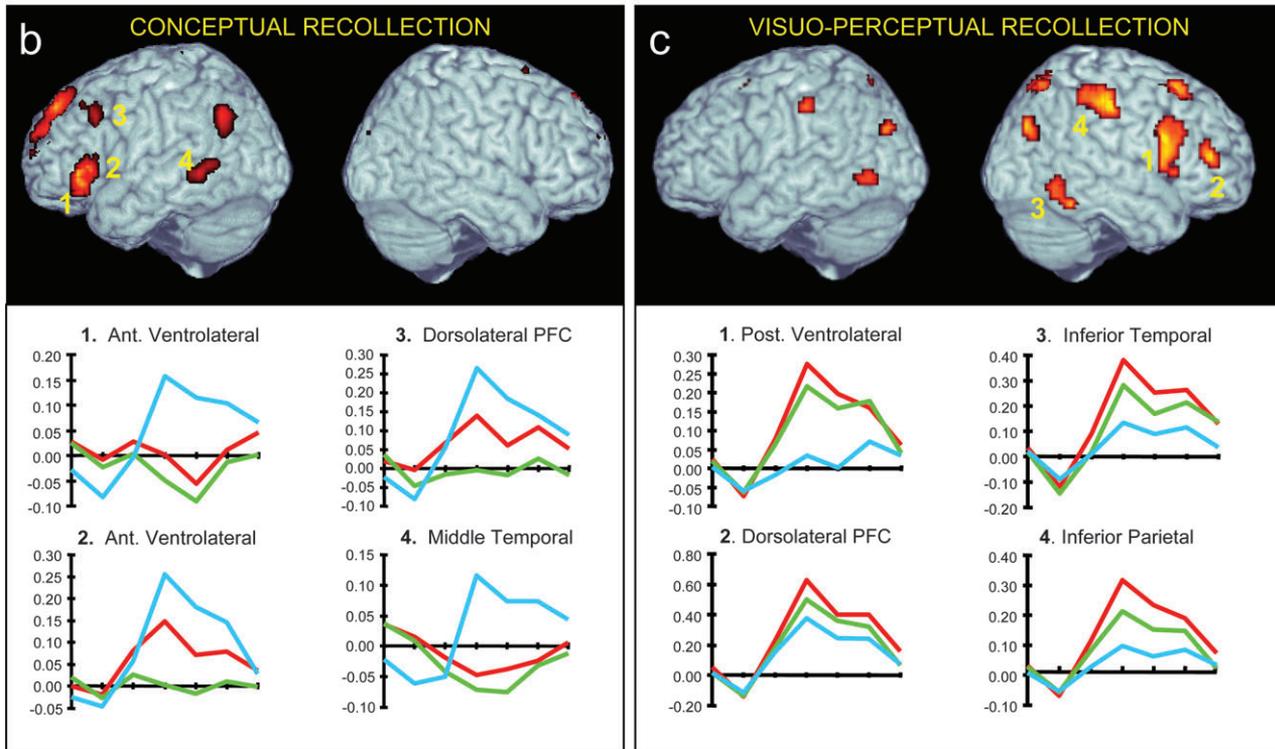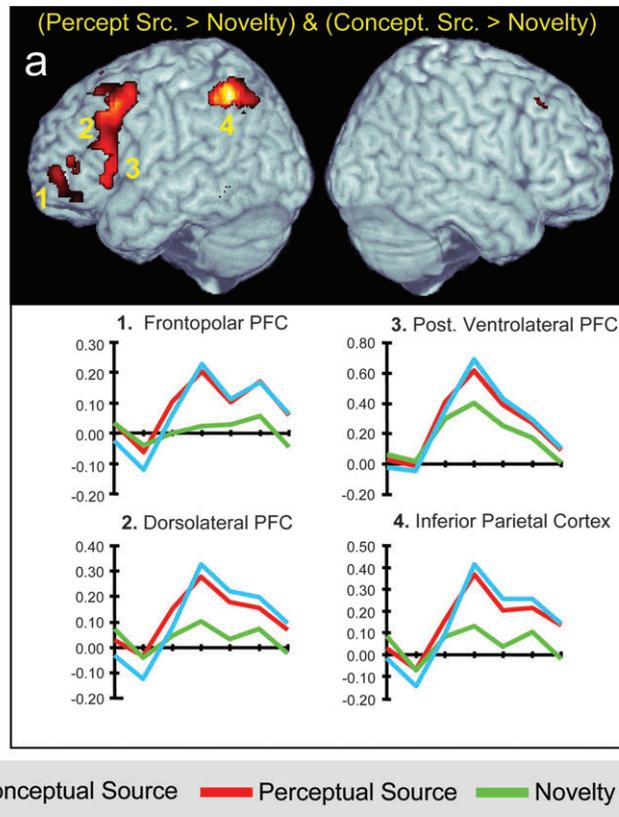
Figure 2. (*a*) Regions demonstrating greater activation for source recollection in comparison to novelty detection, regardless of target domain (conceptual or perceptual). SPM is overlaid on a canonical brain using MRIcro and depicts the overlap between regions demonstrating a greater response during perceptual source versus novelty-detection and a greater response during conceptual source versus novelty-detection (joint probability 0.001). Regions demonstrating any appreciable difference between the two source conditions are excluded from the map (exclusive masking 0.1). Hemodynamic response functions are depicted for representative ROIs, with the ordinate representing percent signal change and tick marks on abscissa representing 2 s time increments following stimulus onset. (*b*) Regions showing a greater response to the pleasant/unpleasant rating task than the living/nonliving rating task at encoding, and a greater response during conceptual than perceptual source retrieval (joint probability 0.001). This pattern is consistent with a role in the conceptual elaboration of probes. (*c*) Regions showing a greater response during perceptual compared with conceptual source retrieval (0.001) consistent with a role in the perceptual elaboration of probes.

Table 2
Regions demonstrating domain-sensitive activation consistent with controlled semantic retrieval[a]

Region	MNI coordinates			Voxels	~BA
Prefrontal cortices					
L anterior ventrolateral (1)[b]	−48	33	−9	40	47
L anterior ventrolateral	−54	30	3	30	47/45
L anterior ventrolateral (2)	−45	27	0	55	47/45
L orbital frontal	−24	24	−21	10	11
L dorsolateral (3)	−42	24	36	29	9
L medial frontal	−9	60	6	60	10
L superior frontal	−9	60	24	72	9/10
L superior frontal	−12	48	48	41	8/9
L superior frontal/dorsolateral	−15	51	27	41	9
medial frontal	0	9	54	13	6
R medial frontal	9	6	54	18	6
R anterior cingulate	12	9	45	9	32
L anterior cingulate	−3	−3	39	14	24
L anterior cingulate	−3	−12	36	10	24
Other regions					
L middle temporal (4)	−60	−39	0	26	22/21
posterior cingulate	−3	−45	33	38	31
L middle temporal	−63	−51	3	31	21
L angular gyrus	−36	−60	33	20	39
L inferior parietal	−48	−60	42	24	40
L precuneus	−3	−60	33	11	7

[a]Joint probability, P < 0.001: (pleasant/unpleasant > living/nonliving rating) + (conceptual > perceptual source retrieval).
[b]Numerals inside parentheses denote regions of interest plotted in Figure 2b. ~BA = approximate Brodmann's area; L = left; R = right.

Table 3
Regions demonstrating domain-sensitive activation consistent with visuo-perceptual attention[a]

Region	MNI coordinates			Voxels	~BA
Prefrontal cortices					
R posterior ventrolateral (1)[b]	54	15	15	61	44/45
R posterior ventrolateral	48	12	24	63	44/9
R anterior ventrolateral	51	21	0	7	47
R dorsolateral	57	24	30	24	9/46
R dorsolateral (2)	51	45	12	27	46
R superior frontal	24	21	57	42	8
L superior frontal	−21	12	48	38	8/6
Other regions					
R fusiform/inferior temporal	45	−45	−18	10	37
R inferior temporal	54	−48	−21	16	37
R inferior temporal (3)	57	−60	−12	23	37
L inferior temporal	−45	−69	−3	14	37
R superior/mid-occipital	42	−78	33	15	19
R superior parietal	15	−72	60	25	7
R superior parietal	27	−69	60	22	7
R superior parietal	21	−60	63	25	7
R superior parietal/precuneus	12	−60	63	24	7
R inferior parietal	45	−39	51	45	40
R inferior parietal (4)	42	−36	42	50	40
R inferior parietal/postcentral	54	−27	48	59	40/2
R postcentral	63	−21	45	28	1
L superior/mid-occipital	−36	−81	30	13	19
L superior parietal/precunues	−12	−66	60	34	7
L inferior parietal/postcentral	−60	−27	45	12	40/2

[a]Probability, P < 0.001: perceptual source retrieval > conceptual source retrieval.
[b]Numerals inside parentheses denote regions of interest plotted in Figure 2c. ~BA = approximate Brodmann's area; L = left; R = right.

technique was to increase power by capitalizing on both study and test contrasts thought to detect differences in conceptual elaboration. Cognitive theory indicates that ratings of pleasantness require greater processing of item specific features compared with ratings that are made with respect to a shared dimension, such as living/nonliving ratings (Hunt and Einstein, 1981; Hunt and McDaniel, 1993). In other words, the basis for deciding that an object is pleasant tends to vary from object to object (e.g. candy, diamonds, freedom), whereas judgements of animacy tend to be made with respect to a reduced, and thus more likely to be shared, set of features across items. Consistent with this assumption, at encoding, pleasant/unpleasant (1694 ms) judgements were executed more slowly than living/nonliving (1419 ms) judgements [$t(14) = 9.18$, $P < 0.001$], suggesting that comparison of the former to the latter encoding trials would identify regions differentially engaged during sustained conceptual analysis (in addition to regions sensitive to other possible task differences). Importantly, at test, the conceptual source task should also require greater analysis of semantic attributes of the probes compared with the perceptual source task and here the reaction times were matched across the two source tasks, further ruling out a duty-cycle/effort interpretation. Accordingly, given this logic underlying the conjunction analysis, controlled semantic analysis mechanisms were isolated by targeting regions showing both greater activity during pleasant/unpleasant versus living/nonliving semantic judgements during the encoding scans, and greater activity during conceptual compared with perceptual source recollection during test scans.

This conjunction analysis revealed that a left lateralized pattern of activity was associated with controlled semantic retrieval (Table 2, Fig. 2b), including left anterior ventrolateral PFC (~BA 47), superior frontal cortex (~BAs 8/10), posterior dorsolateral PFC (~BA9) and middle temporal cortex (~BA 22/21). Critically, left anterior ventrolateral PFC did not contribute to source retrieval in a generalized manner, as this region (i) was

more active when source retrieval tapped conceptual knowledge, but (ii) showed comparable baseline levels of activity during perceptual recollection and novelty detection (Fig. 2b, region 1). Although this region was identified via a study/test conjunction, pair-wise comparisons of peak response magnitudes (6 s post-stimulus onset) confirmed that left anterior ventrolateral PFC responded in a selective manner during memory retrieval. Specifically, direct comparison of conceptual to perceptual source peak activity demonstrated greater activity in the former [$t(13) = 4.16$, $P = 0.001$], whereas perceptual source and novelty trials demonstrated similar response magnitudes that did not extend above baseline [$t(13) = 1.37$, $P > 0.19$].[1] In contrast to this anterior region, in more posterior regions along left ventrolateral PFC, activation also began to emerge for the perceptual source task (Fig. 2b, region 2), until finally at the most posterior extent of left ventrolateral PFC, an above baseline response was also present during novelty detection (Fig. 2a, region 3).

When considered in total, left ventrolateral PFC demonstrated an anterior–posterior gradient of 'conceptual selectivity', with a significantly increasing difference between the responses to conceptual and perceptual recollection in more anterior regions [linear trend of difference, $F(1,13) = 10.01$, $P < 0.01$; Fig. 3]. This pattern is consistent with the hypothesis that the anterior most portion of left ventrolateral PFC subserves a controlled semantic retrieval process that is differentially recruited during attempts to recollect conceptual knowledge (e.g. Wagner et al., 2001a,b; cf. Gold and Buckner 2002). In contrast, the more posterior regions of left ventrolateral PFC demonstrated a more domain-general pattern, and thus may be increasingly engaged as retrieval demands selection regardless of the content domain to be selected (Thompson-Schill et al., 1997; Gold and Buckner, 2002; Buckner, 2003).

The sensitivity of left anterior ventrolateral PFC to the conceptual domain was accompanied by a similar 'conceptual

selectivity' in left middle temporal cortex (Fig. 2b, region 4). Prior data indicate that this region is frequently active when conceptual knowledge must be recovered to meet task demands (Petersen *et al.*, 1988; Klein *et al.*, 1997; Hodges, 2001; Grossman, 2002). As with left anterior ventrolateral PFC, direct comparisons of peak response at test demonstrated greater activity for conceptual versus perceptual source memory [$t(13) = 4.55$, $P < 0.001$] and similar, lowered activity for perceptual source and novelty trials [$t(13) < 1$]. The present data are consistent with the hypothesis that left anterior ventrolateral PFC biases processing in this posterior region in the service of elaborating on (retrieving) conceptual information about the memory probes. This interpretation receives further support from the finding that the magnitude of the difference in peak activity for conceptual versus perceptual source trials in left anterior ventrolateral PFC positively correlated with that in left middle temporal cortex across subjects ($r = 0.60$, $P < 0.05$), suggesting a functional coupling between these structures.

Recollecting Perceptual Details

In comparison with the left lateralized processes engaged during conceptual recollection (Fig. 2b), comparison of perceptual and conceptual recollection revealed increased activity predominantly in the right hemisphere, including right posterior ventrolateral (~BA 44/45) and dorsolateral (~BA 9/46) PFC, together with activity in bilateral inferior temporal (~BA 37), superior (~BA 7) and lateral (~BA 40) parietal cortices, and extrastriate (~BA 19) cortices (Table 3, Fig. 2c).[2] Thus, attempts to recollect the perceptual details of past object encounters engaged a network of regions that is thought to support the allocation of visuo-perceptual attention (right PFC) to inferior

temporal regions known to contribute to object perception and recognition (Bar *et al.*, 2001; Grill-Spector *et al.*, 2001; Bar, 2003). This observation is consistent with a perceptual elaboration hypothesis, wherein attempts to recollect perceptual details of the past depend on the on-line allocation of attention to perceptual details of the retrieval probes. Further supporting this interpretation, the magnitude of the difference in peak response between perceptual and conceptual source trials was positively correlated between right dorsolateral PFC (Fig. 2c, region 2) and right inferotemporal (Fig. 2c, region 3) areas ($r = 0.56$, $P < 0.05$). A similar, marginally significant correlation was observed between right posterior ventrolateral (Fig. 2c, region 1) and this right inferotemporal region ($r = 0.49$, $P = 0.07$). Thus, right PFC and inferior temporal cortex appear to functionally couple during attempts to recollect perceptual episodic details.

Novelty Detection

Of the three retrieval tasks, novelty detection was clearly the least difficult, as indicated by superior accuracy and rapid response times. However, unexpectedly, the regions preferentially engaged during perceptual compared with conceptual recollection also demonstrated elevated activity during novelty detection compared with conceptual recollection (Fig. 2c). Thus, these regions do not track the relative difficulty of the retrieval task.

To further illustrate the overlap between the visuo-perceptual mechanisms engaged during novelty detection and perceptual recollection, we identified regions demonstrating greater activity during (i) novelty detection relative to conceptual source recollection and (ii) perceptual relative to conceptual source recollection using different test scans for each contrast, for each subject. The outcome revealed a striking overlap between the novelty detection and perceptual recollection tasks in the recruitment of right PFC, posterior IT and extrastriate regions, suggesting that these retrieval demands share a common visuo-perceptual attention component (Fig. 4).

Hemispheric Asymmetries during Retrieval

The data suggest that left and right ventrolateral PFC make qualitatively different contributions during episodic retrieval, and that these contributions can be observed even when the format of the test probes remain fixed and task difficulty is similar. For example, as demonstrated in Figure 2a (region 3) and Figure 2c (region 1), left and right posterior ventrolateral PFC
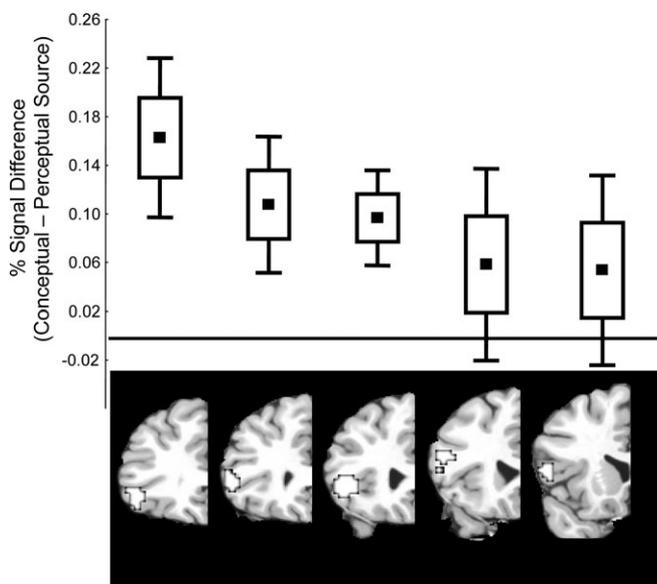
Figure 3. Functional heterogeneity in left ventrolateral PFC during source memory retrieval. Anterior ventrolateral PFC demonstrated a selective increase for conceptual source retrieval in comparison to perceptual source retrieval and novelty-detection. The difference in response between conceptual and perceptual source declined along the anterior-to-posterior axis of left ventrolateral PFC. Each box equals one standard error of the between-subjects mean; box plus whiskers equal two standard errors of the mean.
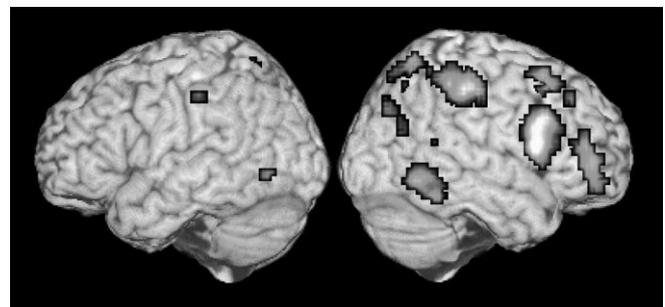
Figure 4. Regions demonstrating an overlap due to common visuo-perceptual attentional demands during novelty detection and perceptual recollection. The overlap is revealed as an increased response for both perceptual source and novelty detection in comparison to the conceptual source task (joint probability 0.001).

(~BA 44) showed qualitatively different patterns of activation. Whereas left BA 44 was similarly active during perceptual and conceptual recollection, with activation during novelty detection being well above baseline, but below these recollection levels right BA 44 showed robust activation during perceptual recollection and novelty detection, with activation during conceptual recollection not differing from baseline.

Given the current theoretical focus on left mid-ventrolateral PFC (~BA 45) as potentially mediating domain-general selection processes (e.g. Buckner, 2002; Thompson-Schill *et al.*, 2003), we also compared the functional patterns in left and right BA 45. To generate an unbiased contrast of hemispheric activity differences in mid-ventrolateral regions, we constructed two ROIs delineating Brodmann's area 45 in both hemispheres using a canonical atlas program (Maldjian *et al.*, 2003) (Fig. 5). ANOVA performed on the peak response (6 s post-stimulus onset) demonstrated a hemisphere × retrieval task interaction [$F(2,26)$ = 39.80, $P < 0.0001$], indicating that the pattern of response across the three tasks qualitatively differed between left and right BA45 (Fig. 5). In left BA 45, both perceptual ($M = 0.27$) and conceptual source ($M = 0.31$) recollection elicited more activity than novelty detection ($M = 0.14$) (Ps < 0.0001), while not reliably differing from each other ($P > 0.18$). In contrast, in right BA 45, both perceptual recollection ($M = 0.21$) and novelty detection ($M = 0.17$) elicited more activity than conceptual recollection ($M = 0.05$) (Ps < 0.0001), while not reliably differing from each other ($P > 0.08$).

Medial Temporal Lobe and Retrieval

The contrast of source recollection versus novelty detection failed to reveal reliable activation within the medial temporal lobe. This null result is difficult to interpret, as several aspects of the forced-choice design may have worked against observing a difference. First, given the high levels of performance across the three test conditions, fMRI data analyses were restricted to correct trials. Thus, contrasts across conditions did not specifically index differences in retrieval success. Secondly, the memory characteristics of the triplets was held constant across all test trials, raising the possibility that MTL processes that are modulated by stimulus novelty or recollection were similarly engaged across the test conditions. Supporting this perspective, a contrast of all retrieval trials to the fixation baseline revealed prominent, bilateral hippocampal activations — although hippocampus was engaged at retrieval, retrieval orientation did not alter this hippocampal response.

Discussion

The present fMRI data demonstrated three distinct outcomes: (i) subregions of left PFC that tracked domain-general source recollection demands (frontopolar, posterior dorsolateral and posterior ventrolateral; Fig. 2*a*); (ii) subregions of left and right PFC that were sensitive to the domain of recollection (left anterior ventrolateral and right ventro/dorsolateral) and that were accompanied by domain-specific posterior cortical responses (left middle temporal and bilateral inferior temporal; Fig. 2*b*,*c*); and (iii) a large degree of response overlap in right PFC and bilateral inferotemporal areas during domain-sensitive perceptual recollection and novelty detection (Fig. 4). Each of these observations provides new insights into the multi-faceted role of PFC control processes in guiding remembrance of the past.

Domain-general source recollection effects were observed in left frontopolar (~BA 10), posterior dorsolateral PFC (~BA 9/8), posterior ventrolateral PFC (~BA 44/45) and lateral parietal cortex (~BA 40), all of which were engaged to a similar degree regardless of whether recollection targeted details that were perceptual or conceptual. Although suggested by others (Buckner, 2003), to our knowledge, this is the first direct demonstration that these regions, while engaged during recollection, are insensitive to large differences in the domain of the to-be-remembered content, and this was the case despite the fact that the domain manipulation resulted in robust effects in other PFC and posterior cortical regions. This finding complements prior observations that activation in these structures does not depend on successful recollection (Ranganath *et al.*, 2000; Dobbins *et al.*, 2003; Kahn *et al.*, 2004), indicating that these regions subserve processes recruited during attempts to recollect rather than processes necessarily dependent upon recollection outcome.

The generalized recollection responses, combined with the minimal response of these regions during novelty detection (Fig. 2*a*), is consistent with the hypothesis that a left-lateralized frontopolar, posterior ventrolateral/dorsolateral PFC and parietal network is engaged when memory decisions require monitoring the sufficiency of contextual recollections. Consistent with prior research, this finding suggests that frontopolar cortex may be particularly crucial when retrieval conditions promote episodic interference, wherein appropriate responding depends on effectively filtering out irrelevant and perhaps intrusive episodic details (Koechlin *et al.*, 1999; Henson *et al.*, 2002) or an ability to maintain an increased focus upon internal representations that differ only marginally with respect to the task goal (Burgess *et al.*, 2005). Alternatively, frontopolar cortex has been argued to subserve the intermediate integration of recovered information with a final goal or decision criterion, such that recollection-based activation in this region may reflect integration demands (e.g. Koechlin *et al.*, 1999; Badre and Wagner, 2004; Bunge *et al.*, 2004). Given this, further research is needed to directly test whether left frontopolar PFC activity requires the presence of conflicting or interfering episodic content. Regardless of the outcome of such investigations, the present findings indicate that engagement of left frontopolar, posterior ventrolateral and posterior dorsolateral regions is not tied to the particular representational domain targeted during recollection.

The second critical finding was the observation that recollection attempts also depend on domain-sensitive mechanisms in lateralized ventrolateral PFC subregions (cf. Schiavetto *et al.*, 2002). In particular, the response pattern of left anterior ventrolateral PFC (~BA 47) qualitatively differed from the domain-general response seen in the proximal left PFC regions. Unlike adjacent frontopolar, posterior dorsolateral and posterior ventrolateral regions that responded similarly across the two recollection tasks, left anterior ventrolateral PFC was selectively active during attempts to recollect conceptual details about the past, with activation during perceptual recollection and novelty detection similarly falling near baseline levels in this most anterior portion of the left ventrolateral region.

Importantly, a pattern of functional heterogeneity was also observed along left ventrolateral PFC (Fig. 3), with selectivity for the conceptual domain increasing in more anterior ventrolateral PFC (Fiez, 1997; Poldrack *et al.*, 1999; Wagner *et al.*, 2000). Consistent with our initial hypothesis, this indicates that left
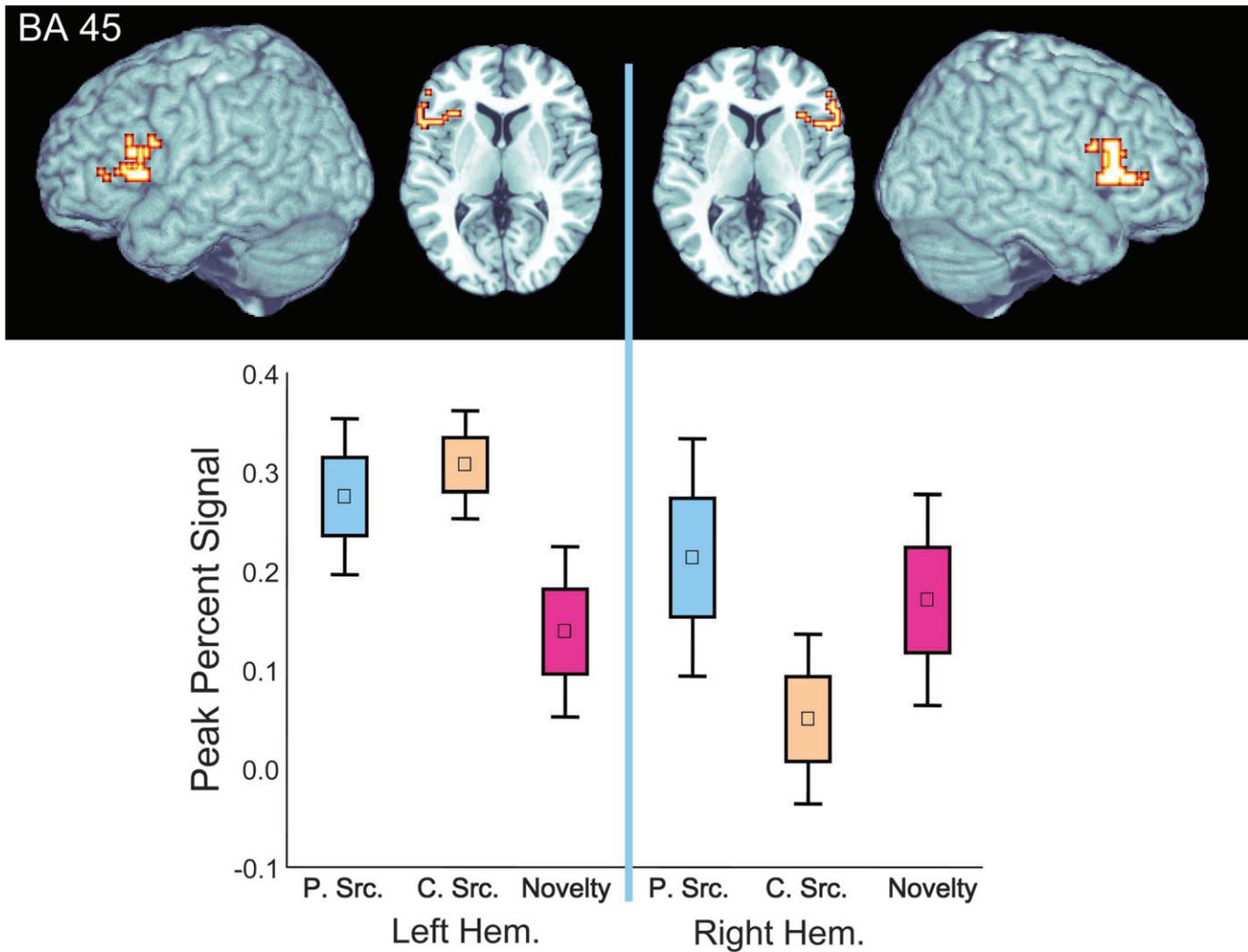
Figure 5. Hemispheric interaction of Brodmann's area 45 during retrieval. The peak response at 6 s post-stimulus onset was calculated for anatomically based ROIs in each hemisphere across the three retrieval tasks (PSrc = perceptual source; CSrc = conceptual source; Novelty = novelty detection). ANOVA demonstrated a qualitatively different response pattern across the two hemispheres. The box plot demonstrates the interaction. (Box equals one standard error of the mean, box plus whiskers correspond to two standard errors.)

anterior ventrolateral processes are recruited during recollection in the service of conceptual elaboration of the probes (e.g. Dobbins *et al.*, 2002), perhaps biasing (or retrieving) relevant long-term conceptual knowledge stored in left middle temporal cortex. By contrast, moving posteriorly along the inferior frontal gyrus, activation began to generalize across memory tasks (Figs. 2*b* and 5), with a mid-ventrolateral region (~BA 45) displaying domain-general source-related activation. Finally, the most posterior ventrolateral region (~BA 44) showed domain-general sensitivity to recollection demands, together with above-baseline activity during novelty detection. This pattern suggests that, in addition to elaborative operations on the probes, recollection may depend on a domain-general selection mechanism that selects target from irrelevant mnemonic details (Thompson-Schill *et al.*, 1997, 1998; Gold and Buckner, 2002; Buckner, 2003) and relies upon a mid-ventrolateral region (~BA 45). In contrast, because novelty detection likely involves minimal competition, the recruitment of the more posterior BA 44 region during both this and the recollection tasks may instead be consistent with the phonological maintenance of retrieval probes in working memory during retrieval attempts (e.g. Dobbins *et al.*, 2002). Accordingly, the present data offer some resolution to the controlled semantic retrieval versus domain-general selection debate regarding left ventrolateral PFC function (Thompson-Schill *et al.*, 1997; Wagner *et al.*, 2001a,b; Badre and Wagner, 2002; Gold and Buckner, 2002), as the two processes appear to differentially depend on distinct subregions within anterior versus mid-ventrolateral PFC. Moreover, these data simultaneously support theories of PFC function that emphasize functional differences between dorsolateral and ventrolateral PFC (Petrides, 1996), together with theories that emphasize differences within anterior and posterior ventrolateral PFC according to representational domain (e.g. semantic versus phonological) (Wagner *et al.*, 2001a).

The final noteworthy outcome relates to the qualitatively different response patterns evinced in right compared with left ventrolateral PFC. In the right hemisphere, both posterior ventrolateral and dorsolateral PFC regions demonstrated greater activity during perceptual relative to conceptual recollection, with the latter task demonstrating near baseline activity levels in

posterior ventrolateral PFC (Fig. 2c). This right PFC pattern, combined with the coactivation of posterior visual association areas, suggests these right PFC regions are engaged when subjects orient attention towards visuo-perceptual, as opposed to conceptual, characteristics of test probes during retrieval attempts.

Overall, the data are consistent with the idea that subjects flexibly elaborate upon either conceptual or perceptual features of retrieval probes depending on the mnemonic goal (Johnson *et al.*, 1993). The implications of these data for the familiarity monitoring account however are less clear. According to that account, right dorsolateral and frontopolar regions are recruited during demanding familiarity discriminations, such as judgements of frequency (Dobbins *et al.*, 2004), relative recency (Dobbins *et al.*, 2003) or low versus high confidence decisions (Henson *et al.*, 2000). Although the present findings might appear inconsistent with this prior suggestion, it may be noteworthy that the right PFC subregions that were differentially engaged during perceptual recollection and novelty detection in the present experiment appear anatomically distinct from the more dorsal and polar right PFC subregions associated with familiarity monitoring. Accordingly, the current data indicate that the more posterior and ventral right PFC subregions identified here are not viable candidates for a generalized familiarity monitoring mechanism since they respond differentially not only as a function of whether subjects are searching for novel stimuli, but also as a function of the type of features (perceptual versus conceptual) that are required to guide the memory decision.

Critically, the present data provide the first evidence, to our knowledge, that right posterior ventrolateral PFC activity tracks the degree to which subjects attend to visuo-perceptual item characteristics during episodic retrieval, regardless of whether those attempts are recollective or familiarity-based (Figs 2c and 5). This finding suggests that during attempts to discriminate novel from familiar objects, subjects may base their decision on perceptual features, engaging a visuo-perceptual bias mechanism in an attempt to increase the gain on the bottom-up (perceptual) inputs activated by the retrieval probes (Hillyard *et al.*, 1998; Reynolds *et al.*, 2003). Gain modulation of perceptual inputs may facilitate familiarity-based discrimination by magnifying differences in the strengths of the memory signals associated with experienced versus novel stimuli. In a similar manner, attempts to recollect perceptual details about a prior encounter with an object may recruit this same bias mechanism to facilitate processing of the perceptual details of the recognition probes in the service of attempting to trigger recollection. From this perspective, ventrolateral PFC control mechanisms are neither 'recollective' nor 'familiarity' based memory processes *per se*, but rather constitute more basic controlled attentional mechanisms that are strategically recruited in the service of remembering depending on the anticipated information value of specific types of representations.

Notes

[1]To assess the functional properties of right anterior ventrolateral PFC, an anatomically defined ROI analysis was performed. As with the voxel-based analyses (which failed to reveal above baseline activation in this PFC region), the ROI analyses revealed no differences in activation magnitudes across the three retrieval tasks, with these magnitudes falling close to baseline levels.

[2]Due to limits on the duration for which fMRI data could be acquired, no functional data were collected during the perceptual orienting study run (i.e. performance of the one-back task). Thus, a conjunction analysis approach to targeting regions sensitive to perceptual orienting was not feasible. Accordingly, we simply contrasted perceptual versus conceptual source trials to highlight regions differentially involved in recollecting perceptual content.

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