

Reviews and perspectives

Left ventrolateral prefrontal cortex and the cognitive control of memory

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Received 13 January 2007; received in revised form 6 April 2007; accepted 13 June 2007

Available online 29 June 2007

Abstract

Cognitive control mechanisms permit memory to be accessed strategically, and so aid in bringing knowledge to mind that is relevant to current goals and actions. In this review, we consider the contribution of left ventrolateral prefrontal cortex (VLPFC) to the cognitive control of memory. Reviewed evidence supports a two-process model of mnemonic control, supported by a double dissociation among rostral regions of left VLPFC. Specifically, anterior VLPFC (~BA 47; inferior frontal gyrus pars orbitalis) supports controlled access to stored conceptual representations, whereas mid-VLPFC (~BA 45; inferior frontal gyrus pars triangularis) supports a domain-general selection process that operates post-retrieval to resolve competition among active representations. We discuss the contribution of these control mechanisms across a range of mnemonic domains, including semantic retrieval, recollection of contextual details about past events, resolution of proactive interference in working memory, and task switching. Finally, we consider open directions for future research into left VLPFC function and the cognitive control of memory.

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Keywords: Memory; Cognitive control; Executive function; Prefrontal cortex

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1. Introduction

Whether determining the appropriate utensil to use at a formal dinner, how much money is necessary for a trip on the subway, or the right words to use when greeting a long absent friend,

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memory informs our behavior. Sometimes knowledge relevant to our goals comes to mind automatically, in a bottom-up fashion, simply by processing cues in our environment. Often, however, relevant experiences from the past or facts about the world do not readily come to mind. In these instances, we must search memory strategically and focus attention on relevant retrieved information. Cognitive control mechanisms, supported by the prefrontal cortex (PFC), allow us to be strategic in making memory subject to our intents and needs. Hence, the cognitive control of memory is fundamental to flexible, goal-directed behavior.

In this review, we focus on the contribution of left ventrolateral prefrontal cortex (VLPFC) to the control of memory. VLPFC encompasses the inferior frontal gyrus anterior to premotor cortex (Brodmann's area [BA] 6) and posterior to the frontal pole (BA 10), and consists of three gross anatomical subdivisions: pars opercularis, pars triangularis, and pars orbitalis. Respectively, these subdivisions correspond approximately to BA 44, BA 45, and the portion of BA 47 along the inferior frontal gyrus, not including caudal orbital frontal cortex. This latter subdivision maps to what Petrides and Pandya (2002b) term area 47/12, noting the homology between area 47 in the human and area 12 in the macaque monkey (Fig. 1).

Functional examination of left VLPFC holds a prominent place in the history of neuropsychology, dating back to Paul Broca's work on non-fluent aphasia (Broca, 1861). More recently, convergent data from a variety of methodologies have highlighted a broader role for VLPFC beyond strict language production (Badre & Wagner, 2002; Buckner, Raichle, & Petersen, 1995; Gabrieli, Poldrack, & Desmond, 1998; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Petrides, 2000; Poldrack & Wagner, 2004; Thompson-Schill, 2003; Thompson-Schill, Bedny, & Goldberg, 2005; Wagner, 1999). In particular, neuropsychological and neuroimaging data have linked left VLPFC

with the cognitive control of memory (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Buckner, 1996; Gabrieli et al., 1998; Petrides, 2002; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). Initial evidence pointed to a fractionation within VLPFC according to representational content (i.e., the *semantic-phonological hypothesis*; e.g., Buckner et al., 1995; Fiez, 1997; Poldrack et al., 1999; Price, Wise, & Frackowiak, 1996). However, as evidence has accumulated, it has become increasingly apparent that anatomically distinct subcomponents of left VLPFC also can be distinguished based on their association with distinct forms of cognitive control. In this review, we consider this more recent evidence for dissociable control processes within left VLPFC, and illustrate how these processes impact behavior across a range of different task domains in which access to memory is critical.

2. Left VLPFC and semantic retrieval

Semantic memory consists of long-term knowledge of facts, word meanings, and object properties (Tulving, 1972). Semantic knowledge is represented in a distributed manner (McClelland & Rogers, 2003), and its storage and retrieval partially depend on inferior and lateral temporal cortical regions (Damasio, 1990; Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Farah & McClelland, 1991; Gorno-Tempini et al., 2004; Martin & Chao, 2001; Nobre, Allison, & McCarthy, 1994; Thompson-Schill, 2003). Retrieval from semantic memory can occur automatically, being triggered by a cue that serves to activate associated concepts. Under such conditions, semantic information may be retrieved via bottom-up inputs that activate representations in temporal cortex, independent of control processes subserved by PFC. While relatively rapid and requiring minimal attention, automatic retrieval is obligatory and non-

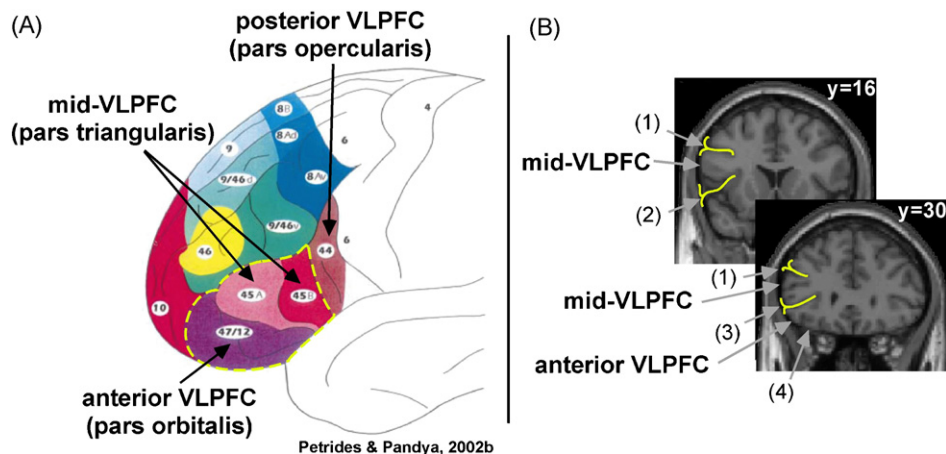


Fig. 1. Anatomical divisions of VLPFC. (A) Schematic representation of the divisions of the prefrontal cortex with cytoarchitectonic areas labeled (adapted from Petrides & Pandya, 2002b). Labels highlight the opercularis, triangularis, and orbitalis subdivisions of the inferior frontal gyrus that correspond to posterior (~BA 44), mid (~BA 45), and anterior VLPFC, respectively. Importantly, the portion of BA 47 that we label anterior VLPFC was distinguished by Petrides and Pandya (2002b) as area 47/12, as it was homologous to monkey area 12 and was distinct from caudal orbital frontal cortex. Moreover, Petrides and colleagues have used the term "mid-VLPFC" to refer to both area 47/12 and area 45. This broader region of VLPFC referred to as "mid-VLPFC" by Petrides and colleagues is highlighted by a yellow outline. Because our aim is to consider functional distinctions between 47/12 and 45 we have adopted "anterior VLPFC" for the former and use "mid-VLPFC" only for the latter. (B) Coronal slices from the MNI canonical brain depict the anatomical boundaries that define mid-VLPFC and anterior VLPFC. Both anterior and mid-VLPFC lie ventral to the (1) inferior frontal sulcus. In caudal slices, mid-VLPFC is bounded ventrally by the (2) horizontal ramus of the lateral fissure. Anterior VLPFC is bounded ventrally and medially by the (4) orbital gyrus.

strategic (Neely, 1991). Hence, exclusive reliance on automatic retrieval may mean that goal-relevant information is not retrieved or suffers from interference due to other retrieved but irrelevant information. Accordingly, cognitive control is often critical for effective use of relevant semantic knowledge.

Left VLPFC has been implicated in cognitive control processes that guide access to relevant information from semantic memory, a role enabled by direct connections from VLPFC to inferior and lateral temporal regions (Crosson et al., 2005; Petrides & Pandya, 2002a; Petrides & Pandya, 2002b). Functional imaging evidence indicates that left VLPFC is more active during conditions requiring goal-directed access to semantic knowledge (Gabrieli et al., 1998; Poldrack et al., 1999), including comparisons of semantic decisions versus word reading (Davis & Johnsrude, 2003; Davis, Meunier, & Marslen-Wilson, 2004; Petersen et al., 1988; Tyler, Bright, Fletcher, & Stamatakis, 2004), semantic versus non-semantic classification of stimuli (Devlin, Matthews, & Rushworth, 2003; Gabrieli et al., 1996; Gold & Buckner, 2002; Kapur et al., 1994; McDermott, Petersen, Watson, & Ojemann, 2003; Noesselt, Shah, & Jancke, 2003; Noppeney, Phillips, & Price, 2004; Otten & Rugg, 2001; Price et al., 1996; Roskies, Fiez, Balota, Raichle, & Petersen, 2001; Ruschmeyer, Fiebach, Kempe, & Friederici, 2005; Scott, Leff, & Wise, 2003; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Wagner, 1999; Wig, Grafton, Demos, & Kelley, 2005; Wig, Miller, Kingstone, & Kelley, 2004), strategically mediated lexical priming versus automatic lexical priming (Giesbrecht, Camblin, & Swaab, 2004; Gold et al., 2006), and even planning semantically guided gestures (i.e., tool use motions) versus control gestures (Johnson-Frey, Newman-Norlund, & Grafton, 2005). Importantly, left VLPFC appears to make necessary contributions to controlled semantic processing, as performance on a variety of semantic tasks is disrupted by damage to left VLPFC (Martin & Cheng, 2006; Metzler, 2001; Thompson-Schill et al., 1998), by intraoperative stimulation of left VLPFC (Klein et al., 1997), and by application of transcranial magnetic stimulation (TMS) over anterior VLPFC (Devlin et al., 2003; Gough, Nobre, & Devlin, 2005; for related findings, see Kohler, Paus, Buckner, & Milner, 2004; Wig et al., 2005).

2.1. A two-process account of rostral left VLPFC functional organization

Building on the observations of others, as well as recent data emerging from our lab, we recently proposed a two-process account of left VLPFC contributions to controlled semantic processing (Badre et al., 2005). This hypothesis distinguishes between a *controlled retrieval* process that activates goal-relevant knowledge in a top-down manner, and a *post-retrieval selection* process that resolves competition between simultaneously active representations (irrespective of whether these representations were activated in an automatic or controlled manner).

Controlled retrieval is necessary to the extent that semantic information relevant to current retrieval goals is not automatically activated during a retrieval attempt (Badre & Wagner,

2002; Wagner et al., 2001). Under such circumstances, a control process that maintains relevant cues or retrieval plans may provide a top-down bias favoring retrieval of relevant knowledge (Johnson & Hirst, 1993; Neely, 1991; Norman & Bobrow, 1979; Raaijmakers & Shiffrin, 1981). Accordingly, when bottom-up cues are insufficient to elicit activation of target knowledge (i.e., automatic retrieval), demands on controlled retrieval increase (Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). Notably, as controlled retrieval directly affects activation of long-term memory representations, activity in temporal cortical regions that store semantic knowledge should be impacted by the action of controlled retrieval.

Automatic and controlled retrieval processes can result in the recovery of multiple representations. Indeed, it is likely not often the case that the right conjunction of cues is present to ensure that only goal-relevant associated knowledge is activated from memory. Rather, it is inherent to the associative structure of memory that calls to memory will often result in the retrieval of more associated information than is relevant to the current task (Anderson & Spellman, 1995; Badre et al., 2005). Importantly, when multiple representations are activated, *post-retrieval selection* is needed to resolve competition among the multiple retrieved representations, allowing the relevant representation(s) to drive decision and action (Fletcher, Shallice, & Dolan, 2000; Moss et al., 2005). Consistent with this perspective, formal models of retrieval often include a second retrieval step that recovers activated information en route to generating a response (Raaijmakers & Shiffrin, 1981). Accordingly, and in contrast to controlled retrieval, selection is required under conditions of competition from among retrieved representations (Badre et al., 2005; Badre & Wagner, 2002; Fletcher et al., 2000; Zhang, Feng, Fox, Gao, & Tan, 2004).

Operationally, selection demands can be manipulated by increasing the number or strength of active competitors. Mechanistically, selection requires the maintenance of goal information in order to bias activation of relevant representations over competing irrelevant representations (Cohen, Dunbar, & McClelland, 1990; Miller & Cohen, 2001; Thompson-Schill et al., 1997). As such, selection may even be critical during calls to memory with minimal controlled retrieval demands, such as object naming when multiple candidate lexemes are associated with an object (Kan & Thompson-Schill, 2004; Levelt, 1999; Moss et al., 2005). Moreover, because selection is posited to operate post-retrieval, selection demands can increase independent of semantic retrieval. In this sense, selection may not operate directly on long-term semantic representations stored in lateral temporal cortex, but rather on mediating tokens or lexical representations that bridge stored knowledge and action. Accordingly, it should be possible to functionally dissociate the neural correlates of post-retrieval selection from activity marking retrieval from long-term memory stores, such as in lateral temporal cortical regions (Thompson-Schill, D'Esposito, & Kan, 1999).

To be explicit, the two-process account of left VLPFC function makes three key claims and associated predictions. (1) Automatic retrieval can occur via processing in posterior cortical regions, independent of PFC-mediated cognitive control. Under

Table 1
Summary of the two-process model of left VLPFC control of memory

	Controlled retrieval	Selection
Operation	Pre/during retrieval	Post-retrieval
Locus of control	Long-term semantic representations stored in lateral temporal cortex	Retrieved tokens or lexical representations
Domain of control	Semantic	General (semantic, phonological, or perceptual)
Control demand	Failure to retrieve goal-relevant knowledge from memory	Conflict between relevant and irrelevant retrieved knowledge
Experimental manipulation	Inversely related to the strength of association between cues and target knowledge	Increases with the number or potency of retrieved competitors OR increases with specificity of retrieval goals
PFC focus	Anterior VLPFC	Mid-VLPFC
Co-varies with lateral temporal cortex	Yes	No

such conditions, retrieval-related activity should be present in posterior structures, but need not be reflected in PFC. (2) Controlled retrieval of conceptual knowledge depends on a distinct left VLPFC mechanism that directly influences activation in conceptual stores, such as lateral temporal cortex, and thus should functionally couple with activity in temporal cortex. Demands on this mechanism will be inversely associated with the degree to which bottom-up cues are effective at activating relevant conceptual knowledge. (3) Selection is engaged post-retrieval and depends on a distinct left VLPFC mechanism that operates on simultaneously active representations, irrespective of whether these representations were retrieved in an automatic or controlled manner. Because this mechanism does not directly activate long-term representations, the left VLPFC region mediating post-retrieval selection need not functionally couple with lateral temporal cortex. Demands on this mechanism will increase when multiple representations compete and when the level of competition from irrelevant representations is high. The distinguishing features of controlled retrieval and selection along with the key predictions of the two-process model are summarized in Table 1.

2.2. Evidence for the two-process account of left VLPFC function

Badre et al. (2005) and Gold et al. (2006) have recently provided evidence in support of the two-process model of left VLPFC function. In both papers, a series of fMRI experiments revealed that controlled retrieval and selection are dissociable control mechanisms supported by separable subdivisions of left VLPFC. As detailed below, controlled retrieval was associated with activity in a ventral and rostral portion of left VLPFC. This subregion, which we term *anterior VLPFC*, corresponds approximately to the portion of BA 47 that includes the pars orbitalis subdivision of the inferior frontal gyrus and appears to map to Petrides and Pandya (2002b) area 47/12 (Fig. 1). By contrast, selection was associated with the portion of VLPFC that approximately corresponds to the pars triangularis subdivision of the inferior frontal gyrus (~BA 45). We refer to this subdivision as *mid-VLPFC* to distinguish it from anterior VLPFC (Fig. 1), though we emphasize that this region lies not only caudal but also dorsal to anterior VLPFC. It is important to note that the

term “mid-VLPFC” has been used by Petrides and colleagues (c.f., Petrides, 2002) to refer to both BA 45 (triangularis) and area 47/12 (orbitalis) so as to distinguish these rostral VLPFC subregions from caudal VLPFC (BA 44) and frontal pole (BA 10). Because the present review explicitly considers how BA 45 functionally dissociates from area 47/12, we use mid-VLPFC to refer only to the dorsocaudal portion of the region labeled as such by Petrides and Pandya (2002b; i.e., BA 45).

Turning to the study by Badre et al. (2005), subjects were presented word cues and had to decide which target from a set of two- or four-target words is semantically related to each cue (Fig. 2). By manipulating the task requirements and the nature of the stimuli, demands on selection and on controlled retrieval were systematically varied. First, selection demands were manipulated by varying the specificity of the semantic judgment, with participants making either a global relatedness judgment (i.e., which of the targets is most globally related to the cue) or a feature similarity judgment (i.e., which of the targets is most similar to the cue with respect to a particular feature, such as color) (Fig. 2A; Table 2). Because the feature judgment entails focusing on a specific goal-relevant subset of retrieved knowledge, namely the instructed feature (e.g., color), feature judgments demand increased selection (Thompson-Schill et al., 1997). fMRI revealed that performance of feature (high selection) versus relatedness (low selection) judgments elicited greater activation in left VLPFC inclusive of mid-VLPFC (~BA 45; pars triangularis), whereas this manipulation did not affect activation levels in left anterior VLPFC (~BA 47; pars orbitalis) nor in left middle temporal cortex (~BA 21) (Fig. 2A) (see also, Thompson-Schill et al., 1997).

Second, within the feature judgment task, a congruency manipulation further taxed selection demands by varying whether automatically retrieved knowledge was relevant or irrelevant (Fig. 2B; Table 2). On incongruent feature trials the distractor was a pre-experimental associate of the cue, but not along the relevant dimension, whereas on congruent trials the pre-experimental associate was the target. Hence, on incongruent trials, the association between the cue and distractor elicited automatic retrieval of information irrelevant to the task, which in turn resulted in increased selection demands due to the increased competition between simultaneously active representations. fMRI revealed that incongruent versus congruent trials

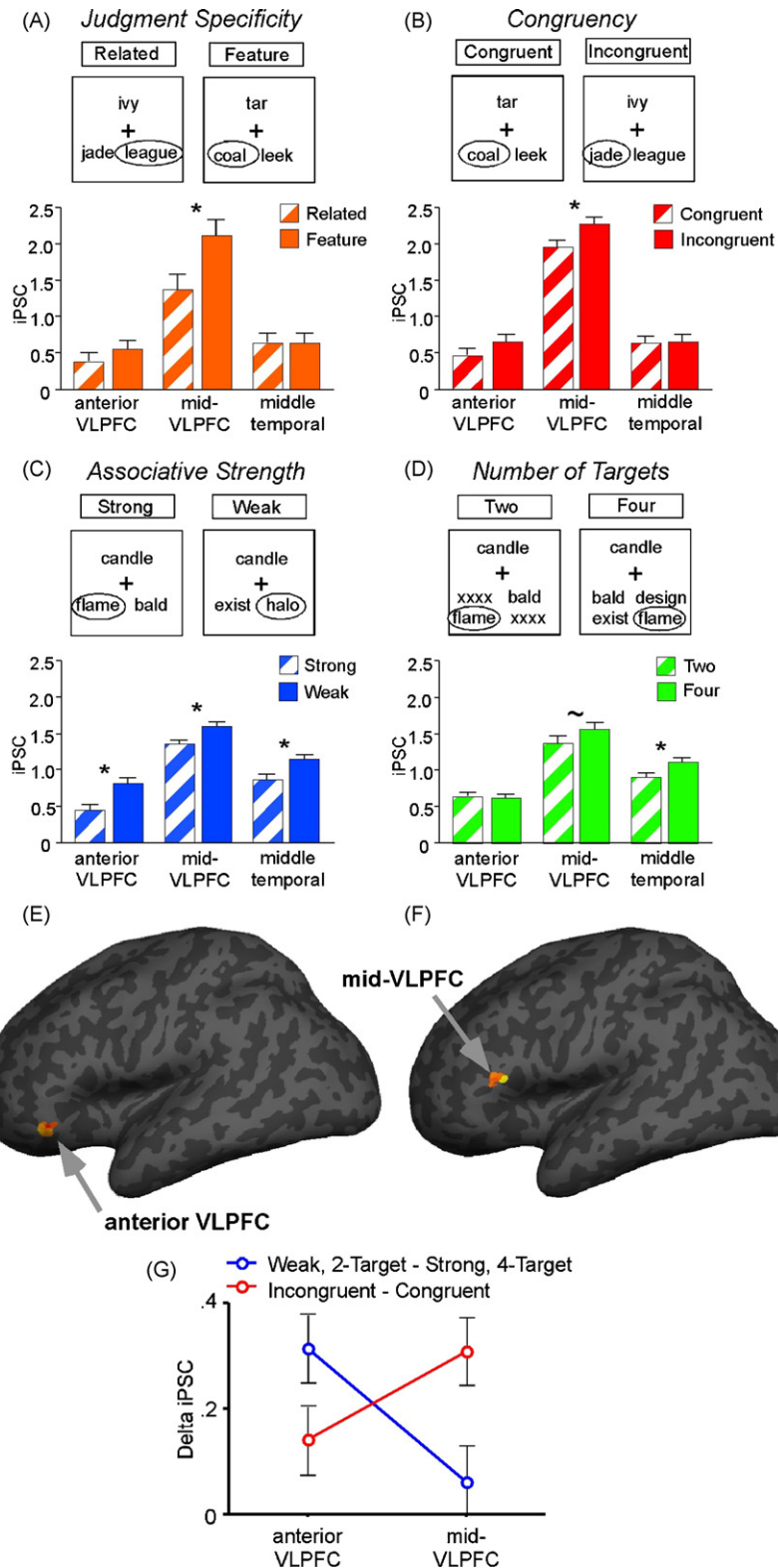


Fig. 2. Results from four manipulations of control during semantic retrieval provide evidence for the two-process model (adapted from Badre et al., 2005). On each trial, subject chose one of two- or four-target words presented beneath a cue word. Schematics depict examples from conditions of (A) Judgment Specificity, (B) Congruency, (C) Associative Strength, and (D) Number of Targets manipulations, with circles indicating the correct target. Graphs in A–D plot integrated percent signal change (iPSC) during each condition from left anterior VLPFC (–54 27 –9), mid-VLPFC (–51 15 33), and posterior middle temporal gyrus (–48 –48 3). Renderings on an inflated MNI canonical depict (E) selective activation in anterior VLPFC from the contrast of weak, two-target versus strong, four-target trials across Badre et al. (2005) and Wagner et al. (2001), and (F) selective activation in mid-VLPFC associated with a meta-variable indexing behavioral variance across the selection manipulations in Badre et al. (2005). (G) A cross-over interaction (i.e., double dissociation) was observed between anterior and mid-VLPFC: the former region showed a greater difference in percent signal change between weak, two-target vs. strong, four-target trials, whereas the latter region showed a greater signal difference between incongruent vs. congruent trials.

Table 2
Summary of stereotaxic coordinates in anterior and mid-VLPFC

Study	Experimental manipulation	Control demand	Anterior VLPFC	Mid-VLPFC
Badre et al. (2005)	Judgment specificity	Selection	XXXX	–45 27 15, –42 33 9
	Congruency	Selection	XXXX	–48 18 18, –54 30 12
	Associative strength	Selection and controlled retrieval	–51 27 –3, –48 30 –12	–48 15 24, –51 21 21, –45 27 15, –48 30 12
	Number of targets	Selection	XXXX	–51 27 15
	Weak, two-target > strong, four-target	Controlled retrieval	–45 27 –15	XXXX
	PCA selection component	Selection	XXXX	–54 21 12
Gold et al. (2006)	Neutral > related	Controlled retrieval	–46 33 –3	XXXX
	Unrelated > neutral	Selection	XXXX	–49 27 24
Dobbins and Wagner (2005)	Conceptual > perceptual source ^a	Controlled retrieval	–48 33 –9, –54 30 3, –45 27 0	XXXX
	Conceptual and perceptual source > novelty detection ^b	Selection	–54 24 –3 ^c	–51 18 6, –51 24 15
Fernandes et al. (2005)	Semantic decision during episodic retrieval > digit decision during episodic retrieval	Selection	XXXX	–50 28 19
Badre and Wagner (2005)	Negative recent > non-recent and positive recent > non-recent	Selection	XXXX	–51 21 6
Badre and Wagner (2006)	Task switch > task repeat (short CSI)	Selection	XXXX	–51 27 6
	Task switch > task repeat	Selection	XXXX	–54 33 18
Average (S.D.)			–48(3) 30(3) –6(6)	–50(3) 25(5) 14(6)

^a Masked by contrast of pleasant/unpleasant > living/non-living.

^b Conjunction of conceptual source > novelty and perceptual source > novelty.

^c Conceptual > perceptual per overlap with –45 27 0; excluded from average anterior VLPFC coordinates.

elicited greater activation in left mid-VLPFC, whereas again there was no effect in left anterior VLPFC nor in middle temporal cortex. These data suggest that lateral temporal cortical regions that store semantic knowledge are insensitive to competition, a pattern consistent with the characterization of selection as operating post-retrieval.

Third, controlled retrieval demands were manipulated by varying the strength of association between the cue and the correct target during global relatedness judgments (Fig. 2C). Greater controlled retrieval is necessary under conditions of weak cue-target associative strength because of diminished bottom-up activation of relevant knowledge (Bunge, Wendelken, Badre, & Wagner, 2005; Wagner et al., 2001). However, varying cue-target associative strength may also increase selection demands because (1) increases in retrieval can result in greater activation of both relevant and irrelevant information from memory, and (2) the weak activation of relevant target knowledge may render this information less competitively viable (Thompson-Schill & Botvinick, 2006). Consistent with this possibility, when cue-target associative strength was weak relative to strong, fMRI revealed greater activation in left VLPFC, inclusive of mid-VLPFC (Fig. 2C; Table 2). Importantly, however, activation was also greater on weak associative strength trials in left anterior VLPFC and posterior middle temporal cortex (Fig. 2C; Table 2), two regions that were insensitive to the selection manipulations (i.e., judgment specificity and congruency). These latter findings suggest that left anterior VLPFC may specifically mediate controlled semantic retrieval by modulating processing in lateral temporal cortex (Bokde, Tagamets, Friedman, & Horwitz, 2001).

Finally, Badre et al. (2005) observed that left middle temporal cortex and mid-VLPFC, but not anterior VLPFC, were more active during trials that contained four versus two targets (Fig. 2D; Table 2). The presence of more targets should result in greater semantic retrieval and thus greater competition, though increasing the amount of knowledge retrieved need not be associated with increased controlled retrieval demands. Indeed, when controlled retrieval was pitted against the amount of semantic knowledge retrieved – contrasting weak, two-target trials (high controlled retrieval/low overall retrieval) with strong, four-target trials (low controlled retrieval/high overall retrieval) – activation was evident only in left anterior VLPFC, with this activation overlapping with that seen in an earlier study using this same contrast (Wagner et al., 2001) (Fig. 2E). Critically, when considered together with the differential sensitivity of mid-VLPFC to the selection manipulations (e.g., congruency), the differential sensitivity of anterior VLPFC to this contrast provides the second half of a double dissociation (Fig. 2G), which was confirmed by a region \times effect interaction ($F(1, 10) = 10.7, p < .01$).

Collectively, the findings of Badre et al. (2005) support the two-process model of left VLPFC function during strategic access to memory. Specifically, when relevant semantic information is not automatically activated, anterior VLPFC provides a top-down influence on posterior cortical regions, facilitating the retrieval of relevant knowledge. By contrast, mid-VLPFC is differentially engaged when competition among retrieved representations necessitates the selection of goal-relevant repre-

sentations from amidst active competitors. As such, selection is likely a general process that may be important during many calls to memory. Consistent with this possibility, a factor analysis revealed a meta-variable that accounted for common behavioral variance across the selection conditions in the Badre et al. (2005) study. Strikingly, left mid-VLPFC was the only region sensitive to all of the factor manipulations that varied selection demands (Fig. 2A–D), and left mid-VLPFC was the only region in which the behaviourally derived meta-variable accounted for functional variance in the BOLD response (Fig. 2F; Table 2).

Recently, Gold et al. (2006) reported that the functional double dissociation between left anterior and mid-VLPFC is replicable and generalizes to other task domains that require controlled retrieval and selection. Specifically, Gold et al. (2006) conducted a series of fMRI studies where demands on automatic retrieval, controlled retrieval, and interference resolution were varied during a lexical decision task. During the key lexical decision trials, participants were presented with a prime word followed by a target letter string, with a 1 s stimulus onset asynchrony (SOA); subjects classified each target as a word or non-word. Target words were either preceded by a related prime (e.g., “Fork” followed by “Spoon”), an unrelated prime word (e.g., “Coat” followed by “Spoon”), or a neutral prime (e.g., “Blank” followed by “Spoon”). Importantly, given the long SOA on these trials, subjects have an opportunity to strategically engage controlled retrieval processes to guide retrieval of prime-associated information in anticipation of the target (Neely, 1991). Accordingly, relative to the neutral prime, for which there was no expectancy about the subsequent target, the related target elicited behavioral facilitation. By contrast, the unrelated prime resulted in interference relative to neutral, as the expectancy elicited by the prime guided retrieval of irrelevant information from memory. Selecting the relevant information upon presentation of the target was thus more demanding due to this competition (Neely, 1991; Neely, Keefe, & Ross, 1989).

With respect to the present discussion, Gold et al. (2006) observed four important fMRI effects (Fig. 3; Table 2). (1) Facilitative priming effects were evident selectively in left anterior VLPFC (related < neutral), and these effects were present only when controlled retrieval was possible (i.e., at long, but not at short, SOAs). This facilitation effect in anterior VLPFC on related relative to neutral trials is consistent with a reduction in the need for controlled retrieval after presentation of the target, due to prior strategic search and priming. (2) Competitive interference effects (unrelated > neutral) were evident selectively in left mid-VLPFC, and are consistent with the increase in irrelevant competitors due to the unrelated cue that is not present on neutral or related trials. (3) Middle temporal cortex activation mirrored the facilitative priming effects evident in anterior VLPFC, but not the interference pattern in mid-VLPFC. (4) In contrast to anterior VLPFC, middle temporal cortex demonstrated facilitative priming effects even at short SOAs, when the influence of controlled retrieval was minimal. Hence, as in Badre et al. (2005), middle temporal cortex was distinguished from anterior VLPFC by its association with automatic retrieval,

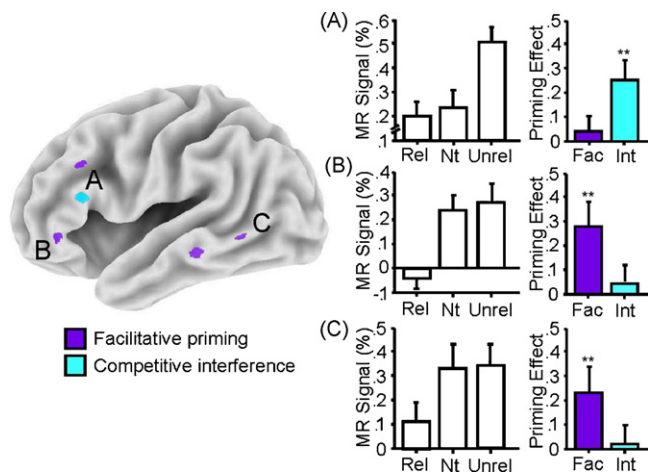


Fig. 3. Double dissociation within left VLPFC from the study of lexical decision by Gold et al. (2006). The left-most graphs plot MR signal from (A) mid-VLPFC ($-54\ 18\ 17$), (B) anterior VLPFC ($-49\ 38\ -2$), and (C) posterior middle temporal cortex ($-54\ -44\ -2$) across related, neutral, and unrelated priming conditions. Facilitative priming (purple) and competitive interference (blue) effects are rendered on a canonical brain, and the corresponding differences in MR signal are plotted in the right-most graphs. Facilitative priming was indexed based on the difference between neutral and related conditions, and was observed in anterior VLPFC (corresponding to the anterior left inferior prefrontal cortex [aLIPFC] designation by Gold et al.) and posterior middle temporal cortex. Competitive interference was computed based on the difference between unrelated and neutral conditions, and was observed in mid-VLPFC (corresponding to the posterior LIPFC designation by Gold et al.)

but activation in this region also tracked the sensitivity of anterior VLPFC to increased controlled retrieval. Moreover, both left anterior VLPFC and middle temporal cortex dissociated from left mid-VLPFC, in that the latter selectively tracked the level of competition between active representations.

The results reviewed here suggest that at least two control mechanisms – controlled retrieval and post-retrieval selection – can operate on semantic representations. Importantly, the observed dissociations suggest that left VLPFC control processes cannot be differentiated simply by their sensitivity to conflict (Thompson-Schill & Botvinick, 2006) or other single dimensions, such as cue ambiguity (e.g., Petrides, 2002). For example, consider that both controlled retrieval and selection could be conceptualized within the bias competition framework, in that both likely bias relevant over competing representations. Indeed, conceptualized in this way, both controlled retrieval and selection could theoretically reduce to a common mechanism, as we have previously speculated (Badre & Wagner, 2002) and as has been more formally considered by others (Thompson-Schill & Botvinick, 2006). However, the dissociation within left VLPFC, taken together with the pattern of activation in left middle temporal cortex, demands an account that would appear incompatible with a single process model. Hence, we propose that left anterior and mid-VLPFC are distinguished on the basis of the representations on which they operate. More specifically, anterior VLPFC appears critical in biasing representations stored in temporal cortical regions, particularly in the lexical/semantic domain (Bokde et al., 2001). Mid-VLPFC, by contrast, appears sensitive to conflict among already retrieved

representations, though at present it is unclear where these representations reside. Moreover, as we will see in the following section, this mid-VLPFC selection process appears to be broadly applicable, generalizing to representations beyond the semantic domain.

3. VLPFC and episodic retrieval

Episodic memory supports conscious remembrance of life events, providing a record of past experiences that, when retrieved, can inform current decision and action (Tulving, 1972, 2002). Broadly defined, episodic memory allows an organism to discriminate between familiar (encountered) and novel stimuli, and to recollect specific event details surrounding a prior encounter with a stimulus (Cohen, Eichenbaum, & Poldrack, 1997; Squire, 1992). Of particular interest for present purposes is recollection, which is thought to occur when a component of a stored episodic representation serves to cue pattern completion, wherein other associated components (items or features) from the encoded event are reinstated (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Norman, 2002). Multiple forms of cognitive control impact episodic recollection (Moscovitch & Winocur, 2002; Shimamura, 1995), including processes subserved by VLPFC (Buckner, 2002; Fletcher & Henson, 2001; Wagner, 1999).

3.1. Controlled retrieval and domain-sensitive episodic remembering

Controlled retrieval mechanisms may influence episodic remembering by biasing retrieval of information in particular knowledge domains, providing control over the cues that serve to trigger pattern-completion (Polyn, Natu, Cohen, & Norman, 2005) and event reconstruction (Addis, Wong, & Schacter, 2007). Broadly consistent with this hypothesis, fMRI data indicate that VLPFC supports domain-sensitive control processes that contribute to episodic remembering, with activation lateralized based on the nature of the retrieval probes (e.g., verbal versus visuo-object; Lee, Robbins, Pickard, & Owen, 2000; Wagner et al., 1998; for a related result, see also Kostopoulos & Petrides, 2003).

Extending earlier findings, Dobbins and Wagner (2005) recently examined whether the neural correlates of episodic recollection differ depending on whether subjects are asked to recollect conceptual or perceptual details about previously encountered objects. A critical component of the task design was that the retrieval probes were held constant across conditions, with only the nature of the to-be-recalled details differing. Specifically, during conceptual recollection, subjects had to remember how they had previously conceptually classified objects (having made a pleasant/unpleasant or a living/non-living judgment at encoding). During perceptual recollection, subjects had to remember a perceptual attribute about previously classified objects (whether the object had appeared in a large or small size at encoding; see also Ranganath, Johnson, & D'Esposito, 2000).

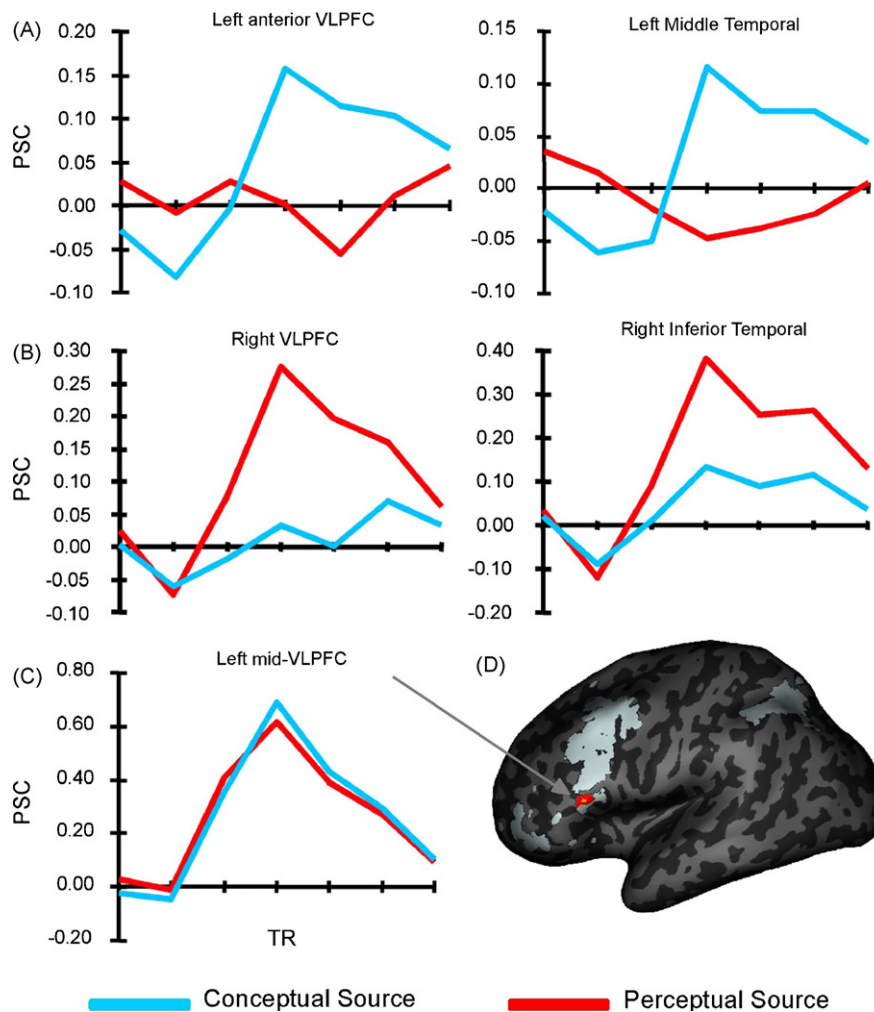


Fig. 4. Activation in VLPFC during episodic recollection of source information (adapted from Dobbins & Wagner, 2005). Graphs plot percent signal change with time (TR units) across conceptual source (blue) and perceptual source (red) decisions. (A) Left anterior VLPFC ($-48\ 33\ -9$) and left middle temporal cortex ($-60\ -39\ 0$) were selectively engaged during attempts to recollect conceptual source details. (B) Right VLPFC ($54\ 15\ 15$) and right inferior temporal cortex ($57\ -60\ -12$) were differentially engaged during attempts to recollect perceptual source details. (C) Left mid-VLPFC ($-51\ 18\ 6$) was engaged to an equivalent extent during conceptual and perceptual source decisions, with these activation levels being significantly greater than that during item recognition (corresponding data function not shown; see Dobbins & Wagner, 2005 Fig. 2A). (D) The contrast of perceptual and conceptual source decisions relative to simple item recognition is rendered in white on an inflated canonical surface. The colored voxels corresponds to those showing a conjunction between this domain-general source recollection contrast and the left mid-VLPFC focus associated with post-retrieval selection in Badre et al. (2005; see Fig. 2F).

Comparison of trials that required conceptual versus perceptual episodic recollection revealed a functional double dissociation (Fig. 4A and B; Table 2). (1) Attempts to recollect conceptual details about a past episode elicited activation in left anterior VLPFC and left posterior middle temporal cortex, with the anterior VLPFC focus converging with that associated with controlled semantic retrieval by Badre et al. (2005). (2) Across-subjects, the magnitude of differential activation in left anterior VLPFC during conceptual versus perceptual recollection correlated with that in left posterior middle temporal cortex, revealing a functional coupling between these structures. (3) By contrast, attempts to recollect visual perceptual details about a past episode with an object elicited activation in right VLPFC and bilateral lateral occipitotemporal cortex. Respectively, these regions have been implicated in mediating attention to visuo-object representations (Courtney, Ungerleider, Keil, & Haxby,

1996; Kelley et al., 1998; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Sala, Rama, & Courtney, 2003) and object perception and recognition (Bar, 2003; Bar et al., 2001; Grill-Spector, Kourtzi, & Kanwisher, 2001). (4) Across-subjects, the magnitude of differential activation in right VLPFC during perceptual versus conceptual recollection correlated with that in bilateral occipitotemporal cortex, revealing a functional coupling between these structures. When considered with respect to the two-process model described above, these results suggest that the controlled retrieval processes mediated by left anterior VLPFC, and also right VLPFC, impact episodic retrieval by biasing processing in distinct representational domains. In this manner, these control processes may specify, elaborate, and/or refine the cues used to probe memory, thereby favoring remembering of event details from goal-relevant knowledge domains.

3.2. Post-retrieval selection and the competitive nature of episodic remembering

While successful episodic retrieval often entails the recollection of multiple details about a past event, under many circumstances the mnemonic objective is very specific. That is, satisfying one's present goal may require decisions based on a particular subset of episodic details. For example, upon encountering a familiar individual, one may need to remember the last place in which the person was encountered, or what the person was previously wearing, or what conversation occurred during the earlier meeting. In such instances, remembering a particular encoded detail (termed the 'source' or 'criterial' detail) guides decisions on how to act (Dodson, Holland, & Shimamura, 1998; Johnson, Hashtroudi, & Lindsay, 1993; Yonelinas, 2002). Characterized in these terms, it becomes clear that many acts of episodic retrieval likely depend on post-retrieval selection (Buckner, 2002). That is, to the extent that recollection results in the retrieval of multiple event details (Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005), when only a subset of these details is relevant to one's goal, selection processes must overcome competition from the irrelevant details to favor the goal-relevant subset.

One test of this hypothesis would be to compare source recollection decisions with item recognition decisions. In contrast to source decisions, item recognition can be based on assessments of item familiarity and/or on the recollection of episodic details. With respect to recollection-based decisions, whereas source decisions require information about a particular episodic detail, it is often the case that any and all recollected details are diagnostic of past encounter with an item and thus all recollected information is relevant to making an item recognition decision. Accordingly, during item recognition, there is typically no need to favor any subset of retrieved information and so post-retrieval selection demands are minimal. Operationally, this logic predicts that post-retrieval selection should be engaged to a lesser extent during item recognition relative to source memory decisions (Buckner, 2002; Dobbins & Wagner, 2005; Velanova et al., 2003). To be clear, this prediction does not follow from a difference in the contribution of recollection versus familiarity to source and item recognition judgments. Even when item recognition is based on recollection of event details (such as when subjects report "remembering" having encountered an item as opposed to "knowing" they have seen it based on a general sense of familiarity), source decisions should still require more post-retrieval selection because only a subset of recollected details are relevant to the source decision. Though this latter prediction awaits empirical support, fMRI studies comparing source versus item recognition decisions have consistently revealed greater activation in left mid-VLPFC (Cabeza, Locantore, & Anderson, 2003; Dobbins, Rice, Wagner, & Schacter, 2003; Nolde, Johnson, & D'Esposito, 1998), though differential activation has also been observed in other left PFC subregions.

Building on these earlier observations, Dobbins and Wagner (2005) recently reported evidence indicating that left mid-VLPFC (Table 2), in particular, mediates post-retrieval selection during source recollection, and that this process is domain-

general. In their experiment, the above-discussed conceptual and perceptual recollection trials were compared to item recognition trials (discriminating novel from familiar objects). With respect to the two-process model of left VLPFC function, this comparison yielded four key findings. (1) Left mid-VLPFC was more active during conceptual source recollection and during perceptual source recollection decisions relative to item recognition decisions. (2) The magnitude of left mid-VLPFC activation did not reliably differ between the conceptual and perceptual source trials, suggesting that post-retrieval selection operates in a more domain-general manner (Fig. 4C and D) (for a related finding of domain-general activity in mid-VLPFC during episodic retrieval, see Sohn et al., 2005). (3) The pattern of activation in left mid-VLPFC dissociated from that in the adjacent, but rostral left anterior VLPFC region, replicating the dissociations between these left VLPFC regions observed by Badre et al. (2005) and Gold et al. (2006). (4) The pattern of activation in left mid-VLPFC also dissociated from that in the right VLPFC regions differentially associated with perceptual versus conceptual recollection attempts.

Convergent evidence regarding the potential importance of left mid-VLPFC selection mechanisms during episodic retrieval comes from recent studies of divided attention at retrieval. In general, dividing attention at retrieval has less of an impact on memory performance than dividing attention at encoding (Craig, Govoni, Naveh-Benjamin, & Anderson, 1996). However, if the secondary task, meant to divide attention, involves representations that overlap with those to be retrieved, then divided attention does impair retrieval substantially (Fernandes & Moscovitch, 2000). From a post-retrieval selection perspective, dividing attention will interfere with retrieval to the extent that performing a secondary task activates representations that compete for processing with to-be-remembered materials. To the extent that representations from the two tasks overlap, left mid-VLPFC may be critical in selecting the subset of representations relevant to the episodic memory decision. Consistent with this hypothesis, episodic retrieval of words was disrupted to a greater extent when attention at retrieval was divided using a secondary task that also involved processing word representations (making animacy judgments) relative to a task the involved processing digit representations (making odd/even number judgments; Fernandes, Moscovitch, Ziegler, & Grady, 2005; Fernandes, Pacurar, Moscovitch, & Grady, 2006; Table 2).

Collectively, these neuroimaging studies of episodic retrieval indicate that activation in left mid-VLPFC tracks domain-general selection demands that are required during source recollection attempts or during attempts to retrieve in the face of interference from other competing active representations. By contrast, activation in left anterior VLPFC tracks demands to recollect conceptual episodic details. Accordingly, the two-process model of left VLPFC function – which initially emerged from studies of semantic memory – also garners support from studies of episodic retrieval. As we discuss in the following two sections, the selection process subserved by left mid-VLPFC also appears central in overcoming mnemonic obstacles to successful performance under conditions that require working memory and task switching.

4. Post-retrieval selection and proactive interference in working memory

Post-retrieval selection is critical when competition is present due to simultaneously active representations. One fundamental form of competition in memory is proactive interference (PI), wherein previous processing (and concomitant representations) negatively influence subsequent processing. Behaviorally, PI leads to slowing and can cause forgetting over long and short intervals (e.g., Anderson & Neely, 1996; Brown, 1958; Keppel & Underwood, 1962; Mensink & Raaijmakers, 1988). At least some forms of PI resemble the type of competition that would require a post-retrieval selection process to be resolved. For example, previous pairing of a cue with a given context may give rise to retrieval of this contextual information upon re-encounter of the cue. If the retrieved contextual details are irrelevant or misleading with respect to the present retrieval goal, then a post-retrieval selection process is necessary to focus attention on the relevant information. Moreover, release from PI, an effect in which a distinguishing change in learned materials results in a rebounding of memory performance (Gardiner, Craik, & Birtwistle, 1972; Wickens, 1970), may depend on cognitive control mechanisms as this effect is extinguished in patients with left PFC lesions (Moscovitch, 1982; Moscovitch, Fernandes, & Troyer, 2001).

The significance of interference for mnemonic performance, or indeed, any sequential or routine behavior, is striking when one considers that PI can occur over very short intervals and following even single exposures to competitor associates. One paradigm demonstrating the cost of PI has been developed within the domain of working memory (Jonides & Nee, 2006; Monsell, 1978). In this paradigm, PI is elicited during short-term item recognition by arranging overlap among consecutive trials of the task. In the traditional item recognition paradigm (Sternberg, 1969), participants are required to maintain a memory set (typically a group of letters) over a delay of a few seconds, and then indicate whether a probe matches (positive) or mismatches (negative) any of the items in the memory set. In the PI-variant of this paradigm, trials are sequenced such that some negative probes – while not present in the current memory set – will have been present in the previous trial's memory set. When this occurs, it takes participants longer to reject such *negative recent* probes relative to rejecting *negative non-recent* probes (i.e., items not present in the current nor in the previous trial's memory set; Jonides & Nee, 2006; Monsell, 1978). Importantly, at the neural level: (1) left mid-VLPFC is more active when subjects reject negative recent probes versus negative non-recent probes (D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Postle, Brush, & Nick, 2004); (2) across-subjects, the behavioral measure of PI (negative recent RT—negative non-recent RT) correlates with the magnitude of differential activation in left mid-VLPFC (Badre & Wagner, 2005; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001); (3) the ability to reject negative recent probes critically depends on left mid-VLPFC, as prefrontal damage inclusive of left inferior frontal gyrus pars triangularis (BA 45) or TMS disruption of this region results in compromised perfor-

mance (Feredoes, Tononi, & Postle, 2006; Thompson-Schill et al., 2002).

How might left mid-VLPFC contribute to interference resolution during working memory? More specifically, given the two-process model of left VLPFC function, can a post-retrieval mechanism that selects from among retrieved contextual details account for the role of mid-VLPFC in resolving short-term PI? Although a number of mechanistic accounts have been considered for this mid-VLPFC effect (Jonides & Nee, 2006), we recently proposed that the same post-retrieval selection mechanism that is sensitive to competition during source recollection (Dobbins & Wagner, 2005) and semantic retrieval (Badre et al., 2005; Gold et al., 2006; Thompson-Schill et al., 1997) is also engaged to resolve PI in working memory (Badre & Wagner, 2005).

In the short-term item recognition task, presentation of a recent negative probe may result in relatively automatic retrieval of a number of contextual details associated with encountering that item in the immediately preceding trial. Such contextual details could include the other items in the previous trial's memory set, attributes about the subject's internal state or about the external environment, etc. These activated representations presumably join the active elements that constitute the contextual details surrounding the current trial. As such, automatically retrieved contextual details from the previous trial serve to compete with the details from the current trial. Given this competition, a mechanism is required to select from amongst the multiple active representations so as to arrive at the correct source attribution for why the negative recent probe seems familiar. That is, as with source memory judgments following long-term retention intervals, left mid-VLPFC may be important to bias selection of relevant representations that permit an accurate source decision over the short-term.

An implication of this theoretical perspective is that *positive recent* probes – items present in both the current and the preceding memory sets – should also elicit competition and place increased demands on post-retrieval selection. That is, while the presence of the probe in the current memory set confers some advantage for the relevant contextual details, nevertheless the automatic retrieval of contextual details from the preceding trial should result in some competition. Accordingly, the post-retrieval selection account predicts that positive recent probes should be associated with increased left mid-VLPFC activation relative to positive non-recent probes. Consistent with this prediction, Badre and Wagner (2005) demonstrated that: (1) positive recent versus positive non-recent probes elicit greater activation in left mid-VLPFC, paralleling that seen in the negative recent versus negative non-recent contrast but to a lesser extent (Fig. 5; Table 2); (2) greater activation was also observed during both positive and negative recent probes relative to non-recent probes in left frontopolar cortex; (3) these left mid-VLPFC and left frontopolar PI effects overlapped with those showing a domain-general source recollection effect in the study by Dobbins and Wagner (2005).

It is worth noting, however, that while the positive recent versus non-recent effect on left mid-VLPFC activation is uniquely predicted by the post-retrieval selection account, there is a

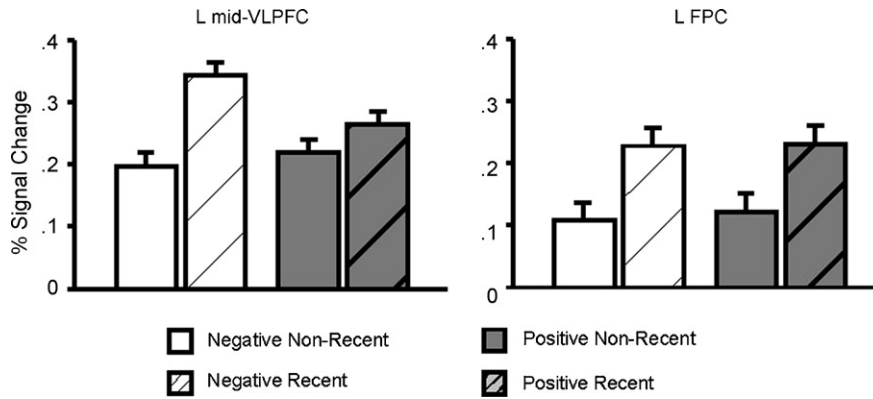


Fig. 5. Activation in left mid-VLPFC is associated with the resolution of PI in working memory. Plots of percent signal change in mid-VLPFC ($-51\ 21\ 6$) and FPC ($-33\ 45\ -9$) show greater activity for non-recent (solid) than recent (striped) for both negative (white) and positive (grey) trials (adapted from Badre & Wagner, 2005).

divergence between this neural response and subject behavior. Specifically, in an insightful review of this literature, Jonides and Nee (2006) noted that despite the increase in left mid-VLPFC on positive recent trials, the behavioral data sometimes show an apparent facilitative effect: RTs for positive recent probes are sometimes faster than for positive non-recent. Thus, whereas there is a correlation between the behavioral expression of PI and the increase in left mid-VLPFC activation during negative recent probes (Badre & Wagner, 2005; Bunge et al., 2001), no such behavioral/neural correlation is present for positive recent probes.

The divergence of the behavioral and imaging consequences of positive recent probes suggests the contribution of multiple mechanisms to the ultimate behavioral outcome. Such a divergence has precedence elsewhere in the cognitive control literature (Milham et al., 2002; Thompson-Schill et al., 1999). For example, congruent trials during the Stroop task, when the color word and the word's color agree, produce a facilitated behavioral response relative to neutral trials. However, whereas DLPFC shows a corresponding decrease in activation on congruent relative to neutral trials (Carter, Mintun, & Cohen, 1995), VLPFC shows an increased response on congruent relative to neutral trials, paralleling that seen on incongruent trials (Milham et al., 2002). Similarly, within the context of a semantic generation paradigm, Thompson-Schill et al. (1999) observed a behavioral/neural dissociation. In their study, subjects were faster to generate a second feature associated with a concept (e.g., generating an action word associated with a noun after having previously generated a color word associated with the noun) relative to when they generated a first feature associated with a concept. This behavioral priming effect, however, was accompanied by *increased* activation in left posterior-to-mid-VLPFC when subjects were generating a second feature relative to generating a first feature. Thompson-Schill et al. (1999) argued that this activation increase reflects the greater selection demands in the former condition due to between-feature competition, and that such competition can occur together with facilitative effects in semantic or perceptual layers that result in overall response speeding. We posit that the neural/behavioral divergence on positive recent trials during the PI-variant of the short-term item

recognition paradigm may reflect a similar distinction, wherein increased competition is present together with facilitation at other levels of stimulus processing. As such, the increase in left mid-VLPFC activation during both negative and positive recent trials, relative to non-recent trials, is consistent with the operation of a post-retrieval selection mechanism that resolves competition between simultaneously active representations.

5. Task-switching, proactive interference, and post-retrieval selection

The ability to strategically access memory is critical for flexible behavior. For example, consider being interrupted, while writing a manuscript, by a phone call from a friend who wants to meet you for dinner in the evening. Previously relevant information, such as what references to include in your introduction, must now give way to a new set of relevant information, such as good restaurants that are close to your friend's home. Given that this newly relevant information must be retrieved, and that its selection may suffer interference from information that had been retrieved to satisfy the earlier goal, then acts of task switching may be understood as controlled acts of memory.

In the laboratory, task switching is studied by comparing episodes during which a task repeats to episodes during which a task changes. Relative to task repeats, task switches result in a behavioral switch cost—an increase in RT and error rates (Logan, 2003; Monsell, 2003). Though a number of theoretical accounts have been proposed to account for this behavioral switch cost, one class of theories suggests that the switch cost may reflect PI due to recent performance of a competing task (Allport & Wylie, 2000; Waszak, Hommel, & Allport, 2003). More specifically, performance of a given task strengthens associations among current task representations. Subsequently, any common cues or responses encountered during performance of a competing task can elicit facilitated retrieval of these strengthened but now irrelevant associates. This results in competition among relevant and irrelevant retrieved representations, and gives rise to a PI-induced switch cost.

Resolving PI during task switching may require post-retrieval selection. Partially consistent with this perspective, damage to

left PFC impairs task-switching performance (Mecklinger, von Cramon, Springer, & Matthes-von Cramon, 1999; Rogers et al., 1998), and a number of fMRI studies of task switching have observed switch-related activation in left VLPFC (Brass & von Cramon, 2002, 2004; Braver, Reynolds, & Donaldson, 2003; Crone, Wendelken, Donohue, & Bunge, 2006; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Dreher & Grafman 2003). Recently, we used a combined computational modeling and fMRI approach to test whether activation in left mid-VLPFC during task switching reflects the role of post-retrieval selection in resolving competition between simultaneously active representations (Badre & Wagner, 2006).

To generate predictions for fMRI, a connectionist model was developed in which a switch cost arises due to PI during a task switch (Gilbert & Shallice, 2002). Given the model’s architecture (Fig. 6A), which consists of three representational layers – task, concept, and response – the switch cost could be reduced through the action of a preparatory control process that increased the bias of the task layer on the conceptual layer. Critically, in the model, the conflict that produces the switch cost arises because units within a given layer compete through mutually inhibitory interactions. This conflict within each representational layer was quantified using a Hopfield energy computation (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Hopfield, 1982), with energy being quantified for different levels of task

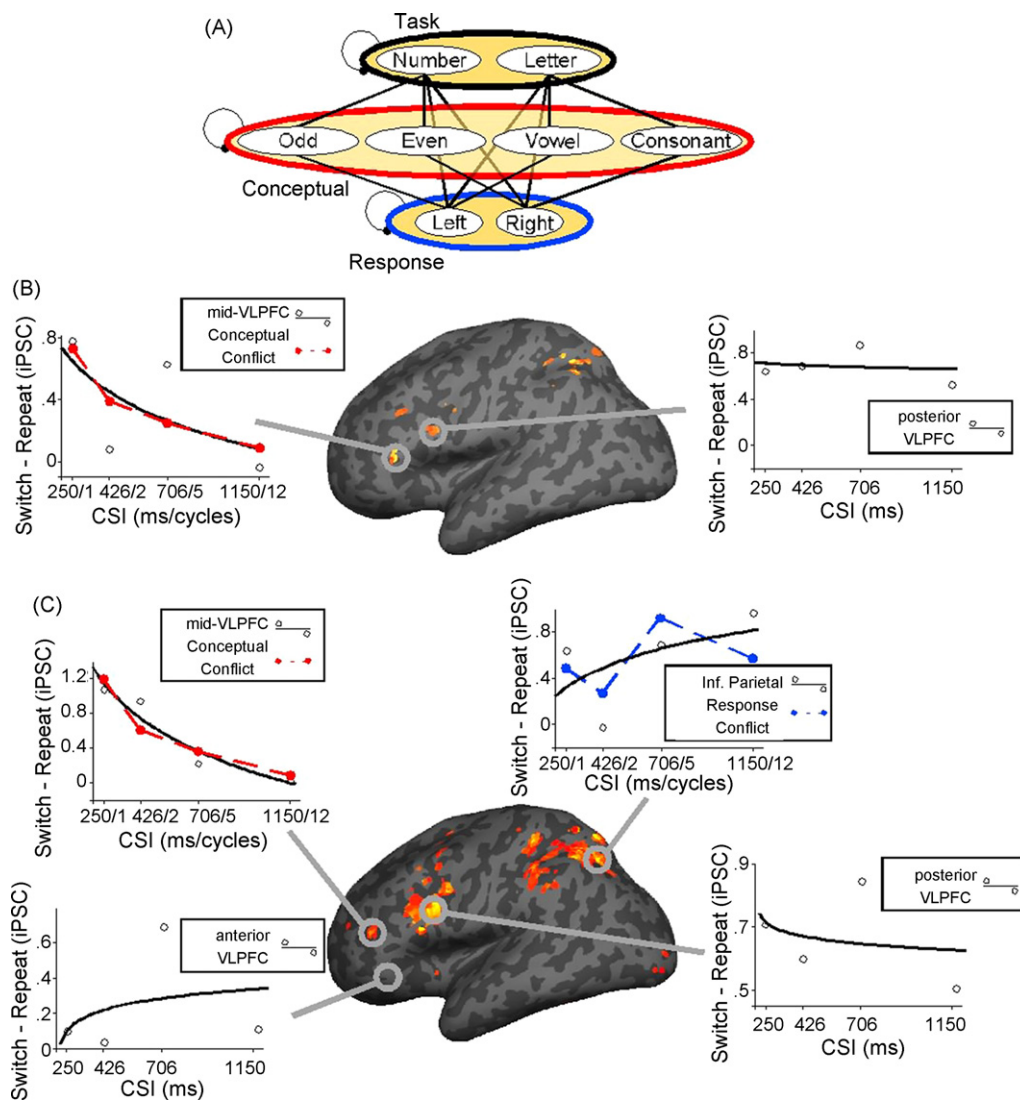


Fig. 6. Activation in left mid-VLPFC is associated with the resolution of PI during task switching. (A) Schematic of task-switching connectionist model depicts three layers of units representing task, conceptual, and response level representations. Reciprocal connections between layers permit activation of a task set, but also elicit PI due to feedback activation of irrelevant nodes. PI is reduced through top-down influence of the task layer on the conceptual layer. (B) The contrast of switch with repeat trials at a short CSI, when conflict is maximal, is rendered on an inflated canonical brain. In contrast to posterior VLPFC (right plot; $-45\ 6\ 27$), in mid-VLPFC (left plot; $-51\ 27\ 6$) the difference in activation between switch and repeat trials was accounted for by the model’s estimate of conceptual conflict (red line). (C) The contrast of switch with repeat across all CSI conditions is rendered on an inflated canonical brain. Activation in mid-VLPFC (left top; $-54\ 33\ 18$) was again explained by the model estimate of conceptual conflict (red line). Activation in inferior parietal cortex (right top; $-51\ -33\ 48$) was explained by the model estimate of response conflict (blue line). By contrast, anterior (left bottom; $-54\ 27\ -9$) and posterior (right bottom; $-45\ 9\ 27$) VLPFC showed no reliable sensitivity to CSI.

preparation (manipulated by varying the cue-to-stimulus interval [CSI] or number of cycles in the model). These measures of conflict were taken as quantitative estimates of the amount of simultaneously active representations in the conceptual and response layers of the model, with an estimate of conflict being computed for each layer at each CSI. We used these measures as predictors for the corresponding fMRI study, where subjects performed the same task used to develop and validate the model.

The central observation from the fMRI study was that the model's index of conflict among active conceptual representations explained the level of activity in left mid-VLPFC (Fig. 6B and C; Table 2).¹ The greater the magnitude of conceptual conflict on switch versus repeat trials, the greater the differential engagement of left mid-VLPFC. Importantly, this correlation was specific to mid-VLPFC, as no other cortical or subcortical structures reliably tracked the magnitude of conceptual conflict across CSIs. Moreover, the conceptual conflict associated with activation in left mid-VLPFC dissociated this region from posterior parietal cortex, which more closely mirrored the model's index of response conflict, thus specifying the level of representation at which PI was being resolved. Finally, in contrast to left mid-VLPFC, when the consequences of switch-related conflict were assessed in left anterior VLPFC (based on the region associated with controlled semantic retrieval), there was no relationship between the model's estimates of competition and left anterior VLPFC function (Fig. 6C).

Building on a rich behavioral literature (Allport, Styles, & Hsieh, 1994; Allport & Wylie, 2000; Gilbert & Shallice, 2002; Waszak et al., 2003; Wylie & Allport, 2000), this combined computational-imaging study indicates that task switching is often an act of interference resolution, wherein selection of relevant representations from other active but irrelevant competitors is required for successful performance. Moreover, the fMRI data provide additional support for a functional dissociation between left mid-VLPFC and anterior VLPFC, a dissociation that appears robust across a range of cognitive domains and task paradigms.

6. Beyond retrieval and selection

Though we view the two-process model to be a parsimonious account of the role of left anterior and mid-VLPFC across a range of tasks requiring the cognitive control of memory, considerable work remains to formally specify these neural mechanisms and to more fully comprehend their broader role in cognition. In this final section, we consider how the two-process model relates to other accounts of left VLPFC function, and highlight open avenues for future research.

¹ It is notable that the mid-VLPFC focus from the contrast of switch vs. repeat at the shortest CSI (Fig. 6B), when competition is at its highest, corresponds precisely to the mid-VLPFC foci highlighted in other studies throughout this review. However, the mid-VLPFC activation from the contrast of switch versus repeat across CSI (Fig. 6C) is somewhat distinct. This focus is more anterior and dorsal, lying partially in the inferior frontal sulcus. Whether this difference simply arises from anatomical variance within a larger mid-VLPFC subregion or reflects a qualitative processing distinction remains unclear.

6.1. Relation to the semantic-phonological hypothesis

A predecessor to the present retrieval/selection parsing of left VLPFC is a proposed distinction between the controlled processing of semantic versus phonological information (Fiez, 1997; Gough et al., 2005; Poldrack & Wagner, 2004; Poldrack et al., 1999; Price et al., 1996). This *semantic-phonological hypothesis* emphasizes a content-based dissociation between left anterior and posterior VLPFC function. The position of mid-VLPFC in this anterior–posterior division has been variable, with researchers sometimes grouping mid-VLPFC with anterior VLPFC and sometimes with posterior VLPFC. Of these two groupings, it has been more common to use posterior VLPFC (or, alternatively, posterior left inferior prefrontal cortex; pLIPC) to refer to the caudal portion of inferior frontal cortex, falling posterior and dorsal to mid-VLPFC, and corresponding to inferior frontal gyrus pars opercularis and portions of premotor cortex (~BA 44/6; see Fig. 1). This region is among those commonly damaged in non-fluent aphasia that are characterized by production, as opposed to comprehension, deficits (Dick et al., 2001; Gorno-Tempini et al., 2004). By contrast, anterior VLPFC (or, alternatively, anterior left inferior prefrontal cortex; aLIPC) has been more commonly used to refer to the rostral two subregions of the inferior frontal cortex (inferior frontal gyrus pars orbitalis and pars triangularis), which correspond to the anterior and mid-VLPFC subregions highlighted in this review. We believe that the evidence reviewed here, together with the dissociative evidence brought to bear in support of the semantic-phonological hypothesis, argue for functional distinctions between the three subdivisions of inferior frontal gyrus (pars opercularis, triangularis, and orbitalis). For example, left mid-VLPFC functionally dissociates from both anterior and posterior VLPFC within the context of task switching (Fig. 6B and C). Moreover, while it is presently unclear whether there are also meaningful functional distinctions even within each of these subdivisions, consideration of this more precise anatomical delineation, along with the mechanistic distinctions derived from the two-process model, may offer some reconciliation of results thought to be inconsistent with the semantic-phonological hypothesis (Clark & Wagner, 2003; Gold & Buckner, 2002).

6.2. Hierarchy and left VLPFC

At a broader level, the retrieval/selection and semantic/phonological distinctions may reflect a general organizing principle of the PFC. In particular, at a coarser level of granularity, it has been proposed that the rostro-caudal axis of PFC reflects a processing hierarchy en route to action (Badre & D'Esposito, submitted for publication; Buckner, 2003; Bunge, 2004; Fuster, 1997, 2004; Koechlin & Jubault, 2006; Koechlin, Ody, & Kouneiher, 2003; O'Reilly, Noelle, Braver, & Cohen, 2002; Petrides, 2005). For example, within VLPFC itself, initial fMRI evidence points to a hierarchical relationship between mid-VLPFC, posterior VLPFC, and premotor cortical function (Koechlin & Jubault, 2006). From this hierarchical perspective, rostral regions of PFC control selection of more abstract action-relevant representations, whereas caudal regions control

selection of representations more concretely tied to an overt response.

The semantic/phonological distinction within left VLPFC readily fits with this rostro-caudal organizing principle, as phonology constrains articulation, and thus may be closer to response-level representations relative to semantic information. Indeed, the role of left posterior VLPFC in phonological processing may reflect its proximity to potential articulatory actions, and such a perspective would appear consistent with single-unit data associating the macaque homologue of BA 44 (opercularis) with orofacial muscle movements, potentially analogous to processes critical for human language production (Petrides, Cadoret, & Mackey, 2005).

When considering the viability of a putative rostro-caudal gradient of abstraction along VLPFC (Buckner, 2003), there remains the question of how to incorporate the present two-process model of left VLPFC function, which might suggest a hierarchal gradient along the rostro-caudal axis. Specifically, as emphasized in this review, the two-process model proposes an anterior to mid-VLPFC flow of information processing, which is compatible with a hierarchical system: anterior VLPFC mechanisms bias retrieval of representations generally in advance of the downstream selection mechanisms mediated by mid-VLPFC that distinguish specific representations for further processing. However, this temporal relationship and potential gradient does not require a hierarchical relationship, and indeed, the distinguishing characteristics of controlled retrieval and selection are not easily described as sub- or superordinate to each other; these being the defining attributes of a hierarchy. Future research may serve to clarify the relationship between the process distinctions captured by the two-process model and broader hierarchy frameworks of the PFC.

6.3. VLPFC and rule-guided behavior

A theme introduced in the above discussion of hierarchy is that VLPFC supports storage or retrieval of stimulus–response contingencies, often termed rules (Bunge, 2004; Passingham, Toni, & Rushworth, 2000). In non-human primates, neurophysiological studies have documented cells in VLPFC, as well as in dorsolateral PFC, that fire in response to particular rules (Wallis & Miller, 2003; White & Wise, 1999). Likewise, lesions to monkey VLPFC, inclusive of orbital frontal cortex, not only impair the ability of animals to behave on the basis of stimulus–response contingencies learned preoperatively, but also impair the acquisition of novel stimulus–response relationships (Bussey, Wise, & Murray, 2001; Murray, Bussey, & Wise, 2000). This learning at least partially depends on an interaction of VLPFC with inferotemporal cortex (Bussey, Wise, & Murray, 2002).

Human neuroimaging studies also support a role for VLPFC in rule processing (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Bunge, 2004; Donohue, Wendelken, Crone, & Bunge, 2005; Sakai & Passingham, 2003; Toni, Rushworth, & Passingham, 2001). In one such experiment (Bunge, Kahn, Wallis, Miller, & Wagner, 2003), a complex rule, defined as a set of stimulus-based contingencies that determined a response,

was compared to a simple rule in which only one contingency determined the response. Comparison of complex and simple rules resulted in greater activation in left VLPFC, and subsequent work has suggested that VLPFC activation may reflect retrieval of rules from long-term stores in lateral temporal cortex (Donohue et al., 2005).

There are two important points to make regarding rule-guided behavior in VLPFC. First, it is not clear that all studies locating rule-based effects in VLPFC are studying the anterior portions of VLPFC that are being highlighted in this review. These distinct posterior portions of VLPFC may be more proximate to premotor cortex and so be more related to the emission of a response than the control of memory (see Petrides, 2005). It is also important to note that, while the relationship between stimuli and responses may be described in terms of rules, this need not require that the representations processed by VLPFC are necessarily sensory-motor associations. Rather, rostral portions of VLPFC may be generally involved in retrieving and selecting more abstract information from memory rather than specific response contingencies, irrespective of whether this information specifies a response or other mnemonic or perceptual representations. From this perspective, rule representations may not hold a privileged status with respect to VLPFC, but rather VLPFC may be more broadly involved in the retrieval and selection of representations that help to guide and constrain action through stored knowledge (Badre, *in press*; Petrides, 2005).

7. Conclusion

The cognitive control of memory permits an organism to strategically bring knowledge to bear on behavior, enabling flexible cognition and action. In this review, we have considered evidence for two cognitive control mechanisms – controlled retrieval and post-retrieval selection – that are supported by left anterior and mid-VLPFC, respectively. These mechanisms appear critical for mnemonic control across several task domains.

While we believe that the two-process model constitutes meaningful progress in delineating left VLPFC function, it is clear that many important open questions remain. For example, whereas the VLPFC mechanisms discussed here were typically left lateralized, a parallel literature has strongly implicated right VLPFC in response selection and inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004; see also Badre & Wagner, 2004). The relation between response inhibition and the mnemonic control mechanisms discussed here remains unclear, particularly in light of the domain-sensitive effects observed in left and right VLPFC during episodic source recollection (Fig. 4). We are optimistic that, as neurophysiological, neuroimaging, and neuropsychological studies continue to build a body of evidence regarding left VLPFC function, so will we gain additional insight into these and other fundamental questions about the function and organization of PFC, including how PFC mediates control over memory.

Acknowledgements

Supported by the NSF (BCS-0401641), NIMH (R01-MH080309-01) the McKnight Endowment Fund for Neuroscience, and the Alfred P. Sloan Foundation. We thank Brian Gold and Ian Dobbins for provision of data figures.

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