The Dynamic Interplay between Cognitive Control and Memory

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ABSTRACT Cognitive control refers to the set of processes that guide thought and action in accordance with current goals. In this chapter we consider the manner in which cognitive control mechanisms guide mnemonic processing. First, we consider the architecture of prefrontal cortex (PFC) and review leading theories of how PFC operations support distinct forms of control. Next, we consider two illustrative and well-characterized situations in which PFC control guides mnemonic processing: (1) when competition between memories creates interference, and (2) when ineffective retrieval cues yield uncertainty. Finally, we consider the ways in which prior mnemonic experiences may reduce future interference and uncertainty, thereby easing the demands placed on PFC control mechanisms. Together, these considerations highlight the dynamic interplay between cognitive control and memory.

Cognitive control refers to the set of processes that guide thought and action in accordance with current goals. Central to higher cognitive function, cognitive control allows organisms to represent task demands, flexibly work with memory, and promote context- and goal-relevant information processing in the face of distraction. Control mechanisms are particularly important in unfamiliar situations or changing environments when acquired knowledge provides either insufficient or inappropriate information to satisfy current demands. The prefrontal cortex (PFC) is a fundamental component of the neural circuitry supporting cognitive control. By orchestrating the influence of past experience on present behavior, PFC mechanisms configure neural processing to optimize behavior.

In this chapter we explore the dynamic interaction between control mechanisms and memory, with a specific focus on prefrontal contributions to cognitive control. We begin with a brief description of the neural circuitry supporting cognitive control, focusing on the anatomy and connectivity of subregions within PFC. Next, we discuss current theories that characterize the mechanisms, functional organization, and regulation of cognitive control. Finally, we review functional neuroimaging and lesion evidence for the interaction between cognitive control and memory, with an emphasis on the interplay between mnemonic uncertainty, interference, and PFC-mediated control functions.

PFC anatomy and connectivity

This chapter will focus on the function of four main subregions within PFC that have been implicated in cognitive control: ventrolateral, dorsolateral, frontalopolar, and medial PFC (figure 48.1). Ventrolateral PFC (VLPFC) corresponds to the inferior frontal gyrus, encompassing pars orbitalis (area 47/12 in Petrides & Pandya, 2002), pars triangularis (~Brodmann’s area [BA] 45), and pars opercularis (~BA 44). Following Badre and Wagner (2007), we refer to pars orbitalis as anterior VLPFC and pars triangularis as mid-VLPFC (note that these two regions have been collectively termed mid-VLPFC by Petrides & Pandya, 2002) and to pars opercularis as posterior VLPFC. Dorsolateral PFC (DLPFC) refers to regions within the middle frontal gyrus (areas 8, 9/46, and 46; Petrides & Pandya, 1999). In humans, the ventral bound of this region is defined by the inferior frontal sulcus and the dorsal bound by the superior frontal sulcus. Frontopolar cortex (~BA 10) corresponds to the most rostral portion of PFC, including portions of middle frontal gyrus. The medial wall of PFC includes portions of BAs 8, 9, and 10 and the anterior cingulate cortex (ACC; BAs 24 and 32). Though anatomically distinct, lateral and medial PFC subregions have been shown to be interconnected both with each other and with more posterior regions of cortex, including medial and lateral temporal cortex and posterior parietal cortex (Petrides & Pandya, 1999, 2002, 2007).

Theories of cognitive control

BIASED COMPETITION A prominent theory of cognitive control proposes that top-down signals derived from PFC bias processing in posterior brain regions in accordance with current task demands (e.g., Cohen & Servan-Schreiber, 1992; Desimone & Duncan, 1995; Miller & Cohen, 2001).
Figure 48.1 Anatomical subdivisions of the PFC. (A) Lateral view of left PFC depicting cytoarchitectonic areas (numbered). Anterior VLPFC corresponds to areas 47/12, mid-VLPFC corresponds to area 45, and posterior VLPFC corresponds to area 44. DLPFC corresponds to middle frontal gyrus including areas 8, 9/46, and 46. FPC corresponds to area 10. (B) Medial view of right PFC. ACC corresponds to areas 24 and 32. FPC corresponds to area 10. VL PPC, ventrolateral prefrontal cortex. DLPFC, dorsolateral prefrontal cortex. FPC, frontopolar cortex. ACC, anterior cingulate cortex. (Reprinted from M. Petrides & D. N. Pandya, 1999. Dorsolateral prefrontal cortex: Comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur. J. Neurosci., 11, 1011–1036. Copyright 1999, with permission from Blackwell Synergy.)

Figure 48.2 Model of PFC and anterior cingulate involvement during performance of the Stroop task. Circles represent processing units, which correspond to a population of neurons assumed to code a given piece of information. Lines represent connections between units, with heavier lines indicating stronger connections. Looped connections with black circles indicate mutual inhibition among units within that layer. In the Stroop task, subjects must name the ink color in which a word is presented, rather than read the word. The presentation of a conflict stimulus (the word “blue” displayed in red ink) activates (indicated by gray fill) input layer units representing “red ink” and the word “blue.” The “colors” task demand unit is activated in PFC (gray fill), representing the current goal to name the color of the ink, and passes activation to the intermediate units in the color-naming pathway (indicated by arrows), increasing the activation of those units and biasing processing in favor of activity flowing along the color-naming pathway. This bias favors activation of the response unit (“red”) corresponding to the color input (red ink), even though the connection weights in this pathway are weaker than in the word-reading pathway that would favor a response based on reading the word (“blue”). By computing the level of conflict (or the presence of simultaneously active representations in the response layer), ACC initially detects the need for this top-down bias from PFC. ACC, anterior cingulate cortex. (Adapted with permission from M. M. Botvinick, T. S. Braver, D. M. Barch, C. S. Carter, and J. D. Cohen, 2001. Conflict monitoring and cognitive control. Psychol. Rev., 108, 624–652. Copyright 2001, American Psychological Association.)
Specifically, the maintenance of task-relevant contextual representations in PFC has been proposed to bias establishment of appropriate mappings between sensory inputs, internal states, and motor outputs. In the absence of cognitive control, behavior is driven in an automatic, bottom-up fashion by representations that are most strongly activated by input cues. However, when weakly established (but task-relevant) representations must be selected in the face of competition from stronger (but task-irrelevant) representations, PFC control signals are thought to bias the flow of information processing to enhance the strength of the relevant representations and overcome the task-irrelevant competitors (Cohen, Dunbar, & McLeod, 1990).

Illustrative of this putative bias mechanism, consider the Stroop paradigm, wherein subjects are presented color words in different ink colors and are asked to name the ink color (figure 48.2). Presentation of a word strongly elicits the prepotent response to read the word, because subjects have more experience reading words than naming the color of word print. Thus, if the ink color is incongruent with the color word (e.g., “BLUE” in red ink), a prepotent response (“blue”) must be overcome in favor of a weaker response (“red”). Biased competition theory proposes that lateral PFC represents the current task goal (e.g., name the ink color) and biases processing in color-naming pathways to favor the weaker but goal-relevant response (Cohen, Dunbar, & McLeod, 1990).

Importantly, top-down bias mechanisms have been argued to support a variety of functions, including working memory, selective attention, controlled retrieval from long-term memory, task switching, response inhibition, and response selection. While the biased competition theory proposes a central mechanism for cognitive control, there may be multiple types of control that differ in their form or domain. In the next sections, we describe several theories that focus on the functional architecture of control and its relationship to the organization of PFC.

**The Dorsal-Ventral Hypothesis** A complementary perspective on cognitive control suggests that dorsal and ventral regions of lateral PFC mediate dissociable, but interactive, forms of control (Petrides, 1994; Owen, Evans, & Petrides, 1996). In this view, control mechanisms supported by VLPFC and DLPFC operate over different loci or types of representations (Petrides, 1996). VLPFC mechanisms have been proposed to support controlled retrieval and selection of long-term knowledge stored in posterior cortices and the maintenance of these representations within working memory, while DLPFC mechanisms have been proposed to support the monitoring and manipulation of the representations retrieved and maintained by VLPFC (e.g., D’Esposito et al., 1998; Petrides, 2002).

Neuroimaging and lesion data support the proposal that DLPFC and VLPFC functionally differ. For example, lesions of mid-DLPFC (areas 9/46 and 46) produce impairments in the ability to order information in working memory (Petrides, 2000), and functional magnetic resonance imaging (fMRI) studies indicate that DLPFC activity increases during complex working memory tasks, such as when working memory loads are high (Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999), as well as when representations held in working memory must be reordered (D’Esposito, Postle, Ballard, and Lease, 1999; Postle, Berger, & D’Esposito, 1999; Wagner, Maril, Bjork, & Schacter, 2001) or updated (Salmon et al., 1996; Garavan, Ross, Li, & Stein, 2000). Similarly, within episodic retrieval tasks, DLPFC activation has often been associated with monitoring retrieved mnemonic information (e.g., Henson, Rugg, Shallice, & Dolan, 2000; Fletcher & Henson, 2001; Dobbins, Foley, Schacter, & Wagner, 2002; Rugg, Henson, & Robb, 2003; Achim & Lepage, 2005; Dobbins, Simons, & Schacter, 2004). In contrast, neuroimaging studies indicate that activity within VLPFC increases during the controlled retrieval and selection of information from long-term memory, as well as in the presence of mnemonic interference (Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; Jonides, Smith, Marschuetz, Koepepe, & Reuter-Lorenz, 1998; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Badre & Wagner, 2002). We will further discuss VLPFC contributions to mnemonic control later.

**Rostrocaudal Hierarchies** In addition to apparent dorsal/ventral dissociations, accumulating evidence suggests that hierarchically organized cognitive control processes map to a functional gradient along the rostrocaudal axis of lateral frontal cortex (Christoff & Gabrieli, 2000; Fuster, 2001; Koechlin, Odly, & Kouneiher, 2003; Wood & Grafman, 2003; Bunge & Zelazo, 2006; Koechlin & Jubault, 2006; Petrides, 2006; Badre & D’Esposito, 2007; Botvinick, 2007; Koechlin & Summerfield, 2007; Badre, 2008). More rostral regions of frontal cortex, inclusive of premotor cortex, are thought to control processing at “lower” levels of representation in the stimulus-action processing hierarchy, such as response selection (figure 48.3). Progressively more anterior regions of frontal cortex are proposed to support control mechanisms that operate upon increasingly “higher” levels of representation (Christoff & Gabrieli, 2000; Badre, 2008), including more abstract higher-order plans or complex schemas. Functional organization along the horizontal axis of lateral PFC has also been characterized as mediating cross-temporal contingencies between past, present, and future events, with caudal PFC mechanisms guiding behavior based upon the immediate context in which a stimulus occurs and more rostral PFC regions...
A  Executive memory  Perceptual memory

B

processing information that is successively more remote in time (Fuster, 2001; Braver, Reynolds, & Donaldson, 2003; Koechlin et al., 2003; Koechlin & Summerfield, 2007).

With its location at the most rostral extent of PFC, frontopolar cortex (FPC; ∼BA 10; figure 48.1) may be positioned at the apex of the putative control hierarchy (Koechlin & Summerfield, 2007). While the precise functions of FPC remain to be determined, neuroimaging studies have consistently observed FPC activation during higher-level cognitive tasks, complex working memory tasks, and episodic retrieval (Fletcher & Henson, 2001; Rammani & Owen, 2004). For example, FPC is recruited when previously selected goals or task-relevant information must be maintained in a pending state until ongoing subtasks are executed (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Braver & Bongiollatti, 2002; Badre & Wagner, 2004; Koechlin & Hyafil, 2007). Similarly, FPC has been associated with higher-order functions such as integrating across multiple sources of information (Christoff et al., 2001; Bunge, Wendelken, Badre, & Wagner, 2004; Rammani & Owen, 2004; Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006; De Pisapia, Slomski, & Braver, 2007) or evaluating the products of internally generated information (Christoff, Ream, Geddes, & Gabrieli, 2003).

REGULATION OF CONTROL. While control mechanisms supported by lateral PFC are thought to drive goal-relevant behavior, equally important are the mechanisms through which control is regulated. Substantial evidence indicates that regions within medial PFC, including the anterior cingulate cortex, serve this modulatory role (but see Fellows & Farah, 2005). Specifically, ACC computations have been alternately proposed to detect the presence of conflict (Botvinick, Cohen, & Carter, 2004; Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000), error likelihood (Brown & Braver, 2003), or uncertainty (Walton, Devlin, & Rushworth, 2004), and to signal lateral PFC mechanisms to increase top-down biasing of task-appropriate representations. For example, ACC may detect the presence of simultaneously active, competing representations (such as conflicting responses elicited by incongruent trials in the Stroop paradigm) and provide feedback signals to lateral PFC that up-regulate control (figure 48.2). Consistent with this proposal, imaging studies have documented functional coactivation of ACC and lateral PFC under situations of response and mnemonic conflict (e.g., Bunge, Burrows, & Wagner, 2004; Badre & Wagner, 2004; Kerns et al., 2004; Kuhl, Dudukovic, Kahn, & Wagner, 2007).

The basal ganglia (BG) have also been implicated in regulating PFC-mediated control processes. For example, in situations of response inhibition it has been argued that the subthalamic nucleus (a component of the BG) interacts with right VLPFC and preSMA such that initiated motor responses can be terminated (Aron & Poldrack, 2006; Aron et al., 2007). It has been argued, through computational models, that PFC-BG interactions also support cognitive operations, such as working memory performance (O’Reilly & Frank, 2006; Hazy, Frank, & O’Reilly, 2007). Specifically, this work has suggested that the BG gate PFC processing depending on task demands, with BG “learning” which PFC mechanisms to gate through dopamine-mediated reinforcement learning. This hypothesis has received support from recent evidence that PFC-BG interactions support working memory performance and that BG activation prior to the onset of working memory trials is predictive of the extent to which task-irrelevant information is successfully gated, or denied processing (McNab & Klingberg, 2008).

Interactions between control and memory

Having surveyed leading theories of how PFC implements cognitive control, we now consider the manner in which prefrontal control interacts with mnemonic operations. However, because there are numerous examples of such interactions across multiple forms and stages of memory and involving multiple PFC subregions (for reviews see Fletcher & Henson, 2001; Wagner, 2002; Buckner, 2003; Simons & Spiers, 2003), we restrict our focus to two examples of PFC involvement in mnemonic processing. Specifically, we consider how VLPFC mechanisms contribute to performance (1) when memory representations interfere with each other and (2) when ineffective retrieval cues yield uncertainty.
INTERFERENCE Interference refers to the processing costs that arise when irrelevant representations compete with goal-relevant representations. For example, when making a trip to the grocery store to purchase a handful of items, one may find that remembering the items of interest becomes remarkably difficult while actually walking down the grocery store aisles, owing to the salience of countless products that are not the items of interest. Overcoming interference requires a mechanism that selects relevant representations from the set of all active representations. Evidence accumulated across semantic memory, working memory, and episodic memory paradigms has led to the hypothesis that left mid-VLPFC, in particular, supports a selection mechanism that plays a fundamental role in resolving mnemonic interference (for review see Badre & Wagner, 2007).

The selection hypothesis of VLPFC function was originally formulated within the context of semantic retrieval. In a seminal paper, Thompson-Schill and colleagues demonstrated that left mid- and posterior VLPFC are engaged to the extent that semantic decisions require selecting goal-relevant information in the face of competition (Thompson-Schill et al., 1997). For example, in one task subjects were shown nouns and required to generate semantically related verbs; critically, some of the nouns were associated with a dominant verb (e.g., “scissors” strongly elicits “cut”; a low-selection situation), whereas other nouns were associated with multiple verbs (e.g., “wheel” may elicit “turn,” “steer,” and “drive”; a high-selection situation). Functional MRI revealed greater left mid- and posterior VLPFC activation during generation under high- relative to low-selection demands (for related findings, see Thompson-Schill, D’Esposito, and Kan, 1999; Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005). Subsequent work demonstrated that damage to left mid- and posterior VLPFC in humans impairs the ability to select relevant semantic representations—specifically when competition is present—establishing the necessity of this region for resolving semantic interference (figure 48.4; Thompson-Schill et al., 1998).

Additional evidence for the role of left mid-VLPFC in resolving interference comes from studies using the interference variant of the Sternberg working memory paradigm (figure 48.5). In this paradigm, each trial requires the encoding and maintenance of a set of stimuli in working memory and determination of whether a subsequently presented test probe is or is not a member of the currently maintained set (trial \( N \)). Interference occurs when the test probe is not a member of the currently maintained set but was a member of the previously maintained set (trial \( N - 1 \))—“negative recent” probes. The now classic finding is that “negative recent” probes elicit greater activation in left mid-VLPFC than do “negative nonrecent” probes—trials requiring the same decision but without interference (figure 48.5; e.g., Jonides et al., 1998; D’Esposito, Postle, Jonides, & Smith, 2005).
**A**

Trial N-1

```
  a  d +  b
    c   +
```

Trial N

```
  e  a + d  +
    f    g
```

**B**

L mid-VLPFC

![Brain image with graphs showing % Signal Change](image)

- Non-Recent
- Recent

**C**

**Response Time**

<table>
<thead>
<tr>
<th>Group</th>
<th>Interference Effect (msec)</th>
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<tr>
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<td>Elderly</td>
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<td>R.C. Patients</td>
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<td>R.C. Controls</td>
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**Error Rate**

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<th>Group</th>
<th>Interference Effect (%)</th>
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<td>Young</td>
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1999; Bunge et al., 2001; Badre & Wagner, 2005; Nee, Jonides, & Berman, 2007). Moreover, the ability to successfully reject negative recent probes is compromised by left mid-VLPFC damage (Thompson-Schill et al., 2002; figure 48.5) or disruption by means of transcranial magnetic stimulation (Federici, Tononi, & Postle, 2006). Mechanistically, it has been argued that rejecting negative recent probes engages left mid-VLPFC because accurate task performance requires identifying (selecting) the relevant context for the familiar negative probe (i.e., that it appeared in the last trial) so that it can be appropriately rejected (Badre & Wagner, 2005; for alternative interpretations, see Jonides & Nee, 2006).

Within the domain of episodic memory, selection to overcome interference likely plays a role during both encoding and retrieval. In a classic PET study, Dolan and Fletcher (1997) measured neural responses during the encoding of word pairs, manipulating the extent to which prior learning interfered with current encoding (i.e., proactive interference). Specifically, subjects first studied a list of word pairs (e.g., “DOG-BOXER”); next, a second list of word pairs was studied, containing either repeated pairs, completely novel pairs, or pairs that partially overlapped with previously studied pairs (e.g., “SPORTSMAN-BOXER”—the proactive interference condition). Dolan and Fletcher observed that left lateral PFC, inclusive of left mid-VLPFC, was highly sensitive to the presence of interference, as this region was differentially engaged when subjects were encoding word pairs that overlapped with previously studied pairs. Additional findings relating left mid-VLPFC to the resolution of proactive interference have been reported in more recent MRI studies of episodic encoding (Fletcher, Shallice, & Dolan, 2000; Henson, Shallice, Josephs, & Dolan, 2002), complementing neuropsychological observations that damage to lateral PFC results in an increased susceptibility to proactive interference (e.g., Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995; Smith, Leonard, Crane, & Milner, 1995). It has been argued that, during episodic encoding, left mid-VLPFC-mediated selection may allow for relevant semantic associations between word pairs to be favored in the face of interference from previously learned, irrelevant associations (Henson et al., 2002).

Left mid-VLPFC engagement has also been observed during episodic retrieval situations that are well characterized as requiring selection. For example, with an increase in the number of competing associates that interfere with retrieval of a target associate, left lateral PFC, inclusive of left mid-VLPFC, displays a corresponding increase in retrieval-related activation (Sohn, Goode, Stenger, Carter, & Anderson, 2003; Sohn et al., 2005; Danker, Gunn, & Anderson, 2006). Likewise, when a retrieval task involves recollecting a specific detail of an encoding event over other possible event details (e.g., as in source memory tasks), left mid-VLPFC, among other regions, is engaged (e.g., Nolde, Johnson, & D’Esposito, 1998; Dobbins et al., 2002; Cabeza, Locantore, & Anderson, 2003; Dobbins & Wagner, 2005; Lundstrom, Ingyar, & Petersson, 2005). Importantly, left mid-VLPFC is distinguished from other lateral PFC regions engaged during source retrieval in that it supports source recollection in a domain-general manner (Dobbins & Wagner, 2005). These data complement neuropsychological observations that patients with lateral PFC damage are particularly impaired at attributing retrieved information to its relevant source [Janowsky, Shimamura, & Squire, 1989].

In summary, extant data provide strong support for the hypothesis that left mid-VLPFC mediates the resolution of interference by selecting goal-relevant representations in the face of competition from irrelevant representations. While we have focused on the role of selection in working-memory, semantic-retrieval, and episodic-memory paradigms, it is worth noting that mid-VLPFC selection has also been asso-
associated with overcoming proactive interference during task switching (Badre & Wagner, 2006). As such, this selection mechanism does not appear to support retrieval, per se (Thompson-Schill et al., 1997); rather, selection likely operates postretrieval such that goal-relevant representations can be favored over goal-irrelevant representations (Badre & Wagner, 2007).

**UNCERTAINTY** While left mid-VLPFC (~BA 45) is thought to support selection between activated representations, a central question is whether there are additional PFC mechanisms that support the top-down activation of representations under other situations of uncertainty. Here we define uncertainty as the situation in which goal-relevant representations are not automatically activated because of ineffective triggering cues. Under such situations, strategic activation, or controlled retrieval, of goal-relevant representations is required to recover relevant knowledge (Wagner, Paré-Blagoev, Clark, & Poldrack, 2001; Badre & Wagner, 2002; Badre et al., 2005; Badre & Wagner, 2007). Extant data indicate that anterior VLPFC (area 47/12) mediates controlled retrieval, with the left homologue differentially supporting such retrieval from semantic memory and the right homologue from visual associative memory.

Evidence for the distinction between selection and controlled retrieval comes from an fmRI study that varied demands on each of these putative control processes (Badre et al., 2005). In that study, controlled retrieval demands were manipulated by varying the strength of the semantic association between a cue and target in a task in which subjects were required to identify semantic associates (targets) of particular cues. For example, identifying the semantic relationship between strongly associated nouns such as “candle” and “flame” places low demands on controlled retrieval, relative to weakly associated nouns such as “candle” and “halo.” The difference in controlled retrieval demands is due to the fact that “candle” is more likely to generate bottom-up activation of the associated concept “flame,” thereby facilitating identification of a semantic relationship; “candle,” however, is less likely to elicit bottom-up activation of weakly associated concepts such as “halo,” meaning that identification of a semantic relationship between these stimuli requires top-down semantic search. Within this same decision task, selection demands were independently manipulated by varying the extent to which irrelevant semantic information was likely to interfere (e.g., by including distracters that were either strong or weakly interfering). Consistent with the selection literature, Badre and colleagues (2005) reported increases in left mid-VLPFC activity as selection demands increased (figure 48.6). In contrast, increases in controlled retrieval demands were associated with increased engagement of left anterior VLPFC and middle temporal cortex—regions that were not modulated by selection (see also Wagner et al., 2001). The coactivation of left anterior VLPFC and middle temporal cortex suggests a frontal-temporal interaction in which left anterior VLPFC provides a top-down bias that activates semantic representations stored in temporal cortex.

Functional dissociations between left mid-VLPFC and left anterior VLPFC have also been observed in the context of short-term semantic priming (Gold et al., 2006) and episodic retrieval (Danker, Gunn, & Anderson, 2008). For example, Gold and colleagues (2006) used a lexical decision priming task to identify regions in which neural processing demands were (1) decreased with the presentation of semantically related primes and (2) increased with the presentation of semantically unrelated (interfering) primes. These two situations provide a compelling parallel between the controlled retrieval and selection distinction explored by Badre and colleagues (2005). For example, when a “related” semantic prime is presented (e.g., “SPOON” as a prime for the target “FORK”), the prime should elicit bottom-up semantic activation that reduces the demand for controlled retrieval once the target appears (i.e., the prime has already activated the relevant semantic information). On the other hand, “unrelated” semantic primes (e.g., “SPOON” as a prime for “COAT”) elicit activation of irrelevant semantic information that may interfere with access to target-related information, thus requiring subsequent selection of relevant target-related information in the face of irrelevant information. Strikingly, the presentation of “related” primes resulted in reduced engagement of left anterior VLPFC and middle temporal cortex, presumably because of reduced controlled retrieval demands, relative to a neutral prime control condition. In contrast, the increased selection demands associated with “unrelated” primes resulted in increased engagement of left mid-VLPFC, relative to the neutral prime condition. Paralleling these findings, Danker, Gunn, and Anderson (2008) observed that left mid-VLPFC and anterior VLPFC functionally dissociate during episodic retrieval, with the former being sensitive to mnemonic competition (fan size) and associative memory strength and the latter being selectively sensitive to associative memory strength.

Together, these studies of semantic retrieval (Badre et al., 2005; Gold et al., 2006) and episodic retrieval (Danker, Gunn, & Anderson, 2008; see also Dobbins & Wagner, 2005) provide compelling evidence for a dissociation between a selection mechanism supported by left mid-VLPFC and a controlled retrieval mechanism supported by left anterior VLPFC that interacts with middle temporal cortex. The argument that left anterior VLPFC, in particular, supports controlled semantic retrieval is also supported by evidence that neural disruption (by means of transcranial magnetic stimulation) of left anterior VLPFC, but not left posterior VLPFC, interferes with semantic—but not phonological—processing (Gough, Nobre, & Devlin, 2005). It should be...
noted, however, that controlled retrieval does not render selection unnecessary. That is, the combination of automatic and controlled semantic retrieval may result in the activation of multiple representations, from which a subset must be selected. Indeed, Badre and colleagues (2005) describe conditions in which both selection and controlled retrieval demands were high, and these situations engaged both left anterior VLPFC and left mid-VLPFC (see also Danker, Gunn, & Anderson, 2008). Thus, while distinct VLPFC subregions appear to support dissociable forms of cognitive control, these functionally separable regions may act in concert when automatic retrieval is insufficient to arrive at mnemonic goals (Kostopoulos & Petrides, 2003, 2008). Moreover, given the dorsal-ventral hypothesis of prefrontal contributions to cognitive control, it is worth noting that PFC correlates of controlled retrieval and selection have been concentrated in VLPFC, rather than DLPFC, subregions.

**Decreased PFC demands through mnemonic suppression and prediction**

Thus far, we have described how the recruitment of PFC control processes facilitates achievement of current mnemonic goals. In this final section, we consider how past experience can favor goal-appropriate representations and reduce future demands on cognitive control. We describe evidence for modulation of control by (1) prior acts of selection that strengthen relevant memories and weaken interfering memories, and (2) experience-dependent plasticity that strengthens memory-based predictions to reduce uncertainty at multiple levels of processing between stimulus input and response output.

**Reduced Interference** Although the presence of competition during retrieval may require PFC mechanisms that implement interference resolution (e.g., Thompson-
Schill et al., 1997; Sohn et al. 2003; Dobbins & Wagner, 2005; Sohn et al., 2005), demands on PFC control mechanisms often change with experience. For example, memories that are repeatedly selected during retrieval accrue a competitive advantage over other memories that are selected against. This advantage stems from both the strengthening of selected memories (e.g., Roediger & Karpicke, 2006) and the weakening of interfering, selected-against memories (M. Anderson, 2003). These adaptive changes in memory strength are thought to “benefit” future processing by favoring memories that are likely to be relevant in the future (J. Anderson, 2007) and reducing interference from memories that are likely to remain irrelevant. Indeed, general support for the processing benefits associated with prior acts of selection comes from fMRI observations of reduced lateral PFC engagement across repeated acts of episodic retrieval relative to initial acts (e.g., Henson et al., 2002; Law et al., 2003). Moreover, electrophysiological evidence indicates that the engagement of PFC during initial selective retrieval is predictive of later forgetting (weakening) of interfering memories, suggesting that reductions in interference occur as a result of prior PFC-mediated mnemonic selection (Johansson, Aslan, Bäuml, Gabel, & Mecklinger, 2007).

Building on these observations, a recent fMRI study examined whether the PFC control mechanisms that support initial mnemonic selection also “benefit”—in terms of reduced subsequent processing demands—from the weakening of interfering memories (Kuhl et al., 2007). At a behavioral level, Kuhl and colleagues (2007) observed that repeated selective retrieval of target memories elicits forgetting of interfering memories, replicating prior observations of retrieval-induced forgetting (M. Anderson, Bjork, & Bjork, 1994; Levy & Anderson, 2002). Critically, when this behavioral effect was related to functional activation during the repeated acts of selective retrieval, the data revealed that the extent to which interfering memories were forgotten was tightly correlated with PFC processing benefits that occurred across the repeated acts of selective retrieval. Specifically, ACC and right anterior VLPFC displayed robust decreases in engagement during future target memory remembering to the extent that interfering memories were forgotten (figure 48.7).

While Kuhl and colleagues’ (2007) data reveal the neural processing benefits of mnemonic filtering (for related findings, see M. Anderson et al., 2004; Depue, Curran, & Banich, 2007), it is important to emphasize that these benefits are obtained only when one’s memory goals remain constant. By contrast, when previously interfering and selected-against memories later become goal-relevant, the weakening that these memories suffered results in increased demands on ACC and right anterior VLPFC processes during their subsequent retrieval (Kuhl, Kahn, Dudukovic, & Wagner, 2008). This dynamic interplay between cognitive control and memory highlights how experience-dependent changes in memory strength and mnemonic competition yield cognitive control benefits and costs, as evidenced by decreasing and increasing demands on PFC control mechanisms during future acts of remembering.

REDUCED UNCERTAINTY Experience-dependent learning also reduces demands on PFC-mediated control by decreasing uncertainty associated with previously encountered stimuli. Illustrative of this point is the phenomenon of repetition priming, a form of nondeclarative (or implicit) memory that is expressed behaviorally as faster reaction times, increased response accuracy, or otherwise biased responding when stimuli are repeatedly processed (Tulving & Schacter, 1990; Roediger & McDermott, 1993). For example, stimulus classification decisions—for example, “Is a horse animate?”—are speeded with repetition, reflecting the behavioral benefits of previous stimulus processing. At the neural level, cortical regions that are active during initial stimulus processing frequently show reduced responses during subsequent stimulus processing (e.g., Raichle et al., 1994; Gabrieli et al., 1996; Schacter & Buckner, 1998; Wiggs & Martin, 1998; Henson, 2003)—a phenomenon that has been referred to as repetition suppression, neural priming, or fMRI adaptation. For example, stimulus repetition in the visual domain is associated with reduced activation in visual cortical areas, as expressed in reduced neural firing rates (Desimone, 1996) and reduced PET/fMRI activation (Wiggs & Martin, 1998; Wagner & Koutstaal, 2002). These neural activation reductions are generally thought to reflect computational savings or more efficient processing in neural networks supporting stimulus perception.

While perceptual priming facilitates processing in sensory cortical regions, other forms of priming are associated with repetition suppression in lateral PFC. In particular, conceptual priming—implicit memory at the level of semantic or conceptual information—is typically associated with activation reductions in left-lateralized frontotemporal regions (figure 48.8), including left VLPFC and regions within inferior and lateral temporal cortex (Demb et al., 1995; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997; Buckner et al., 1998; Gabrieli et al., 1996). Conceptual priming is dissociable from perceptual priming in that conceptual priming is invariant to changes in perceptual input across repetitions (e.g., priming will occur across stimulus modality changes such as auditory to visual), whereas perceptual priming occurs to the extent that there is perceptual overlap across repetitions (e.g., words appearing in the same font or same modality) (Badgaiyan, Schacter, & Alpert, 2001; Carlesimo et al., 2003; Roediger & McDermott, 1993).

Although the repetition suppression in left VLPFC and lateral temporal cortex that accompanies conceptual priming
memory is consistent with the hypothesis that these regions interact during controlled retrieval of semantic information (Badre et al., 2005; Gold, et al., 2006), at present there is debate regarding the processes underlying repetition suppression in these cortical areas. The dominant, or traditional, view is that representations in cortical regions that store conceptual information are “tuned” with experience, such that previously accessed information is more effectively activated during future processing (Wiggs & Martin, 1998; Grill-Spector, Henson, & Martin, 2006; figure 48.8). Several mechanisms have been proposed to support such cortical “tuning” within a population of neurons, including reductions in overall activation (fatigue model), a reduction in the number of responsive neurons (sharpening model), and faster processing or settling time (facilitation model). Viewed in this light, left VLPFC reductions in conceptual priming tasks may reflect reduced control demands owing to increased availability of item-related knowledge.

By contrast, an alternative—though not mutually exclusive—account of repetition suppression in VLPFC is that prior processing of a stimulus results in “stimulus-response” learning that facilitates subsequent mappings between the stimulus and a decision or response (Dobbins, Schnyer, Verfaellie, & Schacter, 2004; Schacter, Dobbins, & Schnyer, 2004). For example, when repeatedly asked, “Is a horse animate?” subsequent performance can be facilitated by direct retrieval of a learned association between the “stimulus” with the relevant “response” (“yes”). Thus, while the retrieval of response information previously associated with a stimulus does not reflect facilitated conceptual processing (rather, it may enable the bypassing of controlled semantic retrieval), “stimulus-response” learning may nonetheless reduce demands on PFC control mechanisms that support decision or response selection (Schacter et al., 2004; Schacter, Wig, & Stevens, 2007).

The role of response learning in conceptual priming tasks has received support from a study by Dobbins, Schnyer, and colleagues (2004). In this study (figure 48.9), stimuli (e.g., “Bulldozer”) were repeatedly semantically classified (e.g., “Larger than a shoebox?”), with the specific classification...
Figure 48.8 Repetition priming paradigm, neural priming effects, and hypothesized mechanisms of “cortical tuning.” (A) In semantic priming tasks, subjects initially study a set of stimuli (e.g., pictures or words), making a semantic decision (e.g., size judgment) about those stimuli. Subsequently, during the critical test phase, semantic decisions are made about previously studied (primed) and novel (unprimed) stimuli. Typically, improved behavioral performance measures (e.g., reaction times and accuracy) are observed for primed compared to unprimed stimuli. (B) Functional MRI scanning during the test phase of a semantic classification priming task revealed activation reductions in fusiform (circled) and left ventrolateral PFC (arrow) for primed compared to unprimed stimuli. (Data from W. Koutstaal, A. D. Wagner, M. Rotte, A. Maril, R. L. Buckner, and D. L. Schacter, 2001, Perceptual specificity in visual object priming: Functional magnetic resonance imaging evidence for a laterality difference in fusiform cortex, Neuroimage, 39, 184–199. Copyright 2001, with permission from Elsevier.) (C) Proposed experience-dependent changes in a neural network representing visual object features. First presentation of a stimulus activates a network of neurons (circles) coding for relevant and irrelevant features of the stimulus. Repeated presentation “tunes” the stimulus representation, reducing the overall firing rate across this network as well as the associated fMRI signal. Possible mechanisms supporting cortical “tuning” in a population of neurons with repeated stimulus presentation include less overall activation (fatigue model), a reduction in the number of responsive neurons (sharpening model), and faster processing or settling time (facilitation model). (Adapted with permission from K. Grill-Spector, R. Henson, and A. Martin, 2006, Repetition and the brain: Neural models of stimulus-specific effects, Trends Cogn. Sci., 10, 14–23. Copyright 2006, with permission from Elsevier.)
A

B

**Priming Phase**

**Cue Reversal Phase**

### PFC

- **% Signal Change**
  - Unprimed
  - Primed

### Fusiform

- **% Signal Change**
  - Unprimed
  - Primed

**Post-stimulus onset times (s)**
decision and the corresponding response either being held constant across repetitions or changed across repetitions (e.g., “Smaller than a shoebox?”). While repetition of a stimulus with the identical decision cue was associated with robust repetition suppression in left VLPFC, repetition of a stimulus with the inverted decision cue was associated with diminished repetition suppression in this region. Because the same conceptual information is accessed across the decision cues, the disruption of priming with cue inversion suggests that the left VLPFC repetition suppression effects typically observed in conceptual priming tasks are at least partially attributable to stimulus-response learning rather than priming of conceptual information. While these data provide an important challenge to accounts of left VLPFC priming that focus only on the reduction in cognitive control demands following cortical tuning of semantic representations, one caveat is that the design used by Dobbins and colleagues covaried repetition at the “decision” and “response” levels. That is, switching the decision from “Larger than a shoebox?” to “Smaller than a shoebox?” requires both a decision switch and a response switch (Schacter et al., 2004; Schnyer, Dobbins, Nicholls, Schacter, & Verfaellie, 2006). Indeed, behavioral evidence suggests that priming at the decision level can be dissociated from response repetition (Schnyer et al., 2007).

Together, extant evidence suggests that prior conceptual processing can reduce demands on PFC control mechanisms during future conceptual processing. However, additional work is needed to establish the extent to which these PFC activation reductions reflect priming at different levels of processing (i.e., conceptual, decision, or response). An intriguing hypothesis is that these distinct levels of learning might give rise to dissociable forms of neural priming. For example, priming at the conceptual level may reduce demands on processing in left anterior VLPFC—a region that has repeatedly been implicated in controlled semantic retrieval—whereas learning at the response level may reduce demands on processing in regions more directly related to response selection (e.g., premotor areas) (Race, Shanker, Clement, & Wagner, 2007). Of additional interest is whether these distinct forms of priming—from higher-level conceptual priming to lower-level response learning—correspond to a representational hierarchy within PFC (Fuster, 2001; Badre & D’Esposito, 2007; Koechlin & Summerfield, 2007), perhaps organized along an anterior (higher-level) to posterior (lower-level) gradient (Race et al.). Insight into these questions will provide a more complete understanding of the multiple ways in which learning from past experiences can reduce future uncertainty, and thus demands on PFC-mediated control.

Conclusion

In this chapter we reviewed influential theories of cognitive control and considered the specific manner in which VLPFC control mechanisms serve to resolve interference and reduce uncertainty during mnemonic processing. While our focus on VLPFC operations reflects the considerable progress that has been made in understanding VLPFC function (for reviews, see Petrides, 2005; Badre & Wagner, 2007), it should be emphasized that other PFC mechanisms work in conjunction with VLPFC to achieve mnemonic goals (for reviews, see Fletcher & Henson, 2001; Wagner, 2002; Buckner, 2003; Simons & Spiers, 2003). For example, it has been argued that while VLPFC supports “active retrieval” of mnemonic representations, DLPFC suberves the complementary role of monitoring mnemonic representations once activated (Petrides, 1996, 2005). To the extent that DLPFC supports the monitoring of mnemonic information (Henson et al., 2000; Fletcher & Henson, 2001; Dobbins et al., 2002; Rugg, Henson, & Robb, 2003; Achim & Lepage, 2005; Dobbins, Simons, & Schacter, 2004), this argument would suggest a hierarchical, but interactive, relationship between VLPFC and DLPFC retrieval operations. Along similar lines, it has been suggested that VLPFC and DLPFC are hierarchically organized during episodic encoding, with VLPFC serving a general role in encoding (e.g., Wagner et al., 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli,
1998), but DLPFC selectively recruited when encoding involves processing the relationship between multiple stimuli (Blumenfeld & Ranganath, 2006; Murray & Ranganath, 2007). Further delineation of the contributions of DLPFC to mnemonic processing, as well as the nature of DLPFC-VLPFC interactions, remains an important avenue for future research. Finally, frontopolar cortex has frequently been implicated in higher-order forms of mnemonic processing (for reviews, see Rugg & Wilding, 2000; Fletcher & Henson, 2001; Buckner, 2003; Ramman & Owen, 2004), though ambiguity remains concerning the specific nature of frontopolar interactions with “lower” forms of mnemonic control. Further advances in our understanding of the interplay between PFC control and mnemonic processing will require consideration of both the computations supported by specific PFC subregions and the manner in which coordinated processing across these subregions allows for the achievement of mnemonic goals.

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