3

Neural Representations Used to Specify Action

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To understand how we use rules to guide our behavior, it is critical to learn more about how we select responses on the basis of associations retrieved from long-term memory and held online in working memory. Rules, or prescribed guide(s) for conduct or action (Merriam-Webster Dictionary, 1974), are a particularly interesting class of associations because they link memory and action. We previously reviewed the cognitive neuroscience of rule representations elsewhere (Bunge, 2004; Bunge et al., 2005). In this chapter, we focus mainly on recent functional brain imaging studies from our laboratory exploring the neural substrates of rule storage, retrieval, and maintenance. We present evidence that goal-relevant knowledge associated with visual cues is stored in the posterior middle temporal lobe. We further show that ventrolateral prefrontal cortex (VLPFC) is engaged in the effortful retrieval of rule meanings from long-term memory as well as in the selection between active rule meanings. Finally, we provide evidence that different brain structures are recruited, depending on the type of rule being represented, although VLPFC plays a general role in rule representation. Although this chapter focuses primarily on the roles of lateral prefrontal and temporal cortices in rule representation, findings in parietal and premotor cortices will also be discussed.

LONG-TERM STORAGE OF RULE KNOWLEDGE

Posterior Middle Temporal Gyrus Is Implicated in Rule Representation

In a previous functional magnetic resonance imaging (fMRI) study focusing on rule retrieval and maintenance, we observed activation of left posterior middle temporal gyrus (postMTG) [BA 21], as well as left VLPFC (BA 44/45/47), when subjects viewed instructional cues that were associated with specific rules (Bunge et al., 2003) [Fig. 3–1]. Although both postMTG and VLPFC were sensitive to rule complexity during the cue period, only VLPFC was sensitive to rule complexity during the delay.

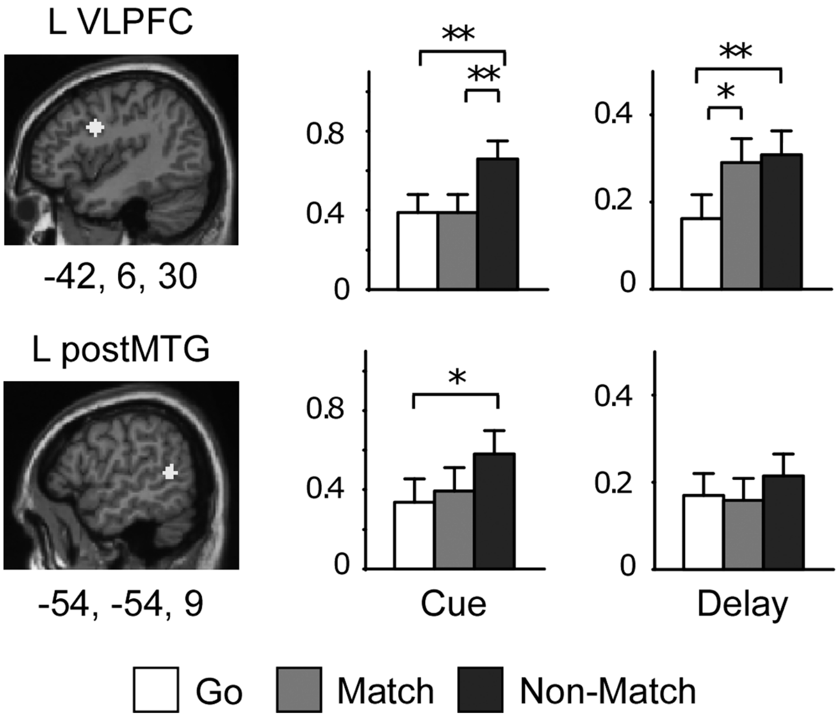

Figure 3–1 Brain activation related to the retrieval and maintenance of rules uncovered by functional magnetic resonance imaging (Bunge et al., 2003). Both left ventrolateral prefrontal cortex (L VLPFC) [BA 44/47] and left posterior middle temporal gyrus (L postMTG) [BA 21] were modulated by rule complexity during the Cue period, but only the left VLPFC continued this pattern into the Delay period. $^{**}p < .01$; $^{*}p < .05$. (Adapted from Bunge et al., 2003, *Journal of Neurophysiology*, 90:3419–3428, with permission from the American Physiological Society).

On the basis of evidence that semantic memories are stored in lateral temporal cortex and that VLPFC assists in memory retrieval (e.g., Gabrieli et al., 1998; Wagner et al., 2001), we proposed that left postMTG might store rule knowledge over the long term, and that VLPFC might be important for retrieving and using this knowledge (Bunge et al., 2003). However, it is clear that postMTG is not specifically involved in storing explicit rules for behavior; rather, the literature on tool use and action representation suggests that this region more generally represents action-related knowledge associated with stimuli in the environment (see Donohue et al., 2005).

In ongoing research, we aim to reconcile the disparate views of postMTG function emerging from the semantic memory literature (i.e., a general role in semantic memory) and the action representation literature (i.e., a more specific role in action-related semantic representation). A recent study from our laboratory is consistent with the latter view, although a definitive answer awaits further experiments.

Intriguingly, our focus in left postMTG was close to a region that is believed to represent knowledge about actions associated with manipulable objects (Chao et al., 1999; Martin and Chao, 2001). A large body of research has shown that this region is active when subjects prepare to use a tool, mentally conceptualize the physical gestures associated with tool use, make judgments about the manipulability of objects, generate action verbs, or read verbs as opposed to nouns (for reviews, see Johnson-Frey, 2004; Lewis, 2006).

Although most of these studies involved visual stimuli (images or words), one group of researchers found that postMTG was engaged by meaningful relative to meaningless environmental sounds (Lewis et al., 2004), and for tools relative to animals (Lewis et al., 2005). Thus, the role of postMTG in storing mechanical or action-related knowledge about stimuli extends to the realm of auditory information; it is unclear whether it also extends to other modalities. Given that we likely acquire most of our action-related knowledge through vision and audition, one might expect that a region that specifically represents action-related knowledge would not be modulated by other modalities. However, the possibility that postMTG is engaged by other stimulus modalities remains an open issue, and we know of no functional brain imaging studies or studies of anatomical connectivity that speak to this issue.

In our rule study, unlike the action knowledge studies mentioned earlier, participants used recently learned arbitrary mappings between abstract cues (nonsense shapes or words) and task rules. This finding suggests that left postMTG plays a broader role in action knowledge than previously assumed. Rather than specifically representing actions that are non-arbitrarily associated with real-world objects, left postMTG also represents high-level rules that we learn to associate with otherwise meaningless symbols.

Explicitly Testing for Involvement of Left PostMTG in Rule Representation

We sought to further test the hypothesis that left postMTG represents rule knowledge in an fMRI study in which subjects viewed a series of road signs from around the world, and considered their meanings (Donohue et al., 2005). We had two reasons for selecting road signs as experimental stimuli: (1) they are associated with specific actions or with guidelines that can be used to select specific actions; and (2) they allow us to examine the retrieval of rule knowledge acquired long ago. As such, these stimuli enabled us to ask whether prefrontal cortex (PFC) [in particular, VLPFC] would be recruited during passive retrieval of action knowledge associated with well-learned symbols.

The road sign study involved "Old" signs that subjects had used while driving for at least 4 years, and "New" signs from other countries that they were unlikely to have been exposed to previously (Fig. 3–2*A*). Of these New signs, half were "Trained" (i.e., subjects were told their meaning before scanning, but

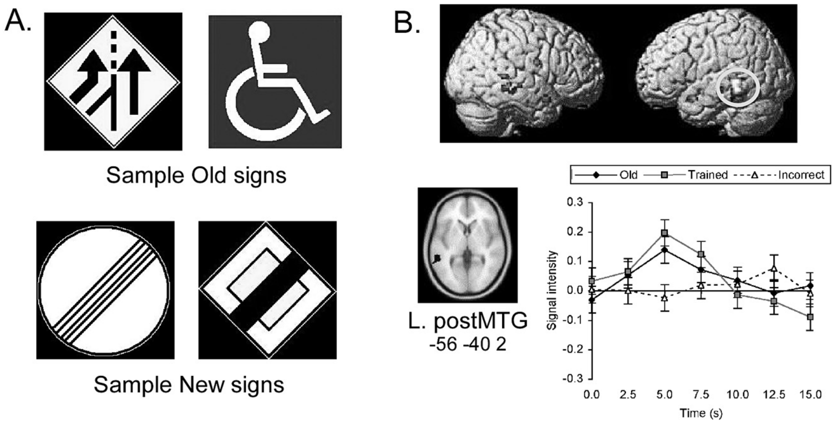

Figure 3–2 Retrieving well-known and recently learned behavioral rules from long-term memory (Donohue et al., 2005). *A.* Domestic, well-known ("Old") and foreign, generally unknown ("New," "Learned") signs were used in the study. *B.* Activation in left posterior middle temporal gyrus (L postMTG) [BA 21; *circled*] was identified in a group contrast comparing all correct trials relative to fixation. *Inset.* Activation in this region was specifically modulated by whether participants knew the meaning of the sign, *not* by when the participant learned the meaning of the sign. (Adapted from Donohue et al., 2005, *Neuroimage*, 26, 1140–1149, with permission from Elsevier).

had had no experience using them to guide their actions). The other half of the new signs were "Untrained"—in other words, subjects had viewed them before scanning, but were not given their meaning. We predicted that left postMTG would be active when subjects successfully accessed the meaning of Old and Trained signs, but not when subjects viewed signs whose meaning they did not know ("Incorrect" trials, of which the majority would be Untrained).

Just as predicted, left postMTG was more active when subjects passively viewed signs for which they knew the meaning than for signs that were familiar, but not meaningful to them (Fig. 3–2*B*). This contrast also identified several other regions, and all were located in the lateral temporal lobes. However, the largest and most significant focus was in the predicted region of left postMTG. Notably, unlike regions in lateral PFC, this region was insensitive to level of experience with the signs—it was engaged equally strongly for correctly performed Old and Trained signs (Fig. 3–2*B, inset*). Thus, it appears that left postMTG stores the meanings of arbitrary visual cues that specify rules for action, regardless of when these cues were originally learned or how much experience one has had with them. This pattern of activation suggests two points: (1) activation of the correct representation in temporal cortex contributes to remembering the sign's meaning; and (2) these temporal cortex representations can be activated either through effortful, top-down processes involving VLPFC or through automatic, bottom-up means (controlled retrieval of rule-knowledge by VLPFC is discussed later).

PostMTG: Action Knowledge, Function Knowledge, or Both?

Although left postMTG has been implicated in tasks that promote retrieval of action knowledge, it has been noted that left postMTG is located near the posterior extent of the superior temporal sulcus, a region associated with representation of biological motion (Chao et al., 1999; Martin and Chao, 2001). Furthermore, this region is engaged when subjects think about how living entities move (Tyler et al., 2003). These observations raise the following question: Does left postMTG represent knowledge about specific *movements or actions* associated with a visual stimulus, or does it represent semantic memories associated with an object, such as—in the case of manipulable objects—knowledge about its *function*?

To address this question, we designed an fMRI study to investigate whether the left postMTG is sensitive to an object's function (functional knowledge) or how the object moves when one uses it (action knowledge) [Souza and Bunge, under review]. Participants viewed photographs of common household objects, such as a pair of scissors. The task was a 2 × 2 factorial design, manipulating whether or not one had to retrieve knowledge about a specific type of object, as well as the domain of cognitive processing required: verbal or visual-spatial (Fig. 3–3*A*).

Based on an instruction that they received on each trial, participants were asked to do one of the following: (1) imagine themselves using the object in a typical way (Imagery); (2) consider how they would describe the purpose of the object to another person (Function); (3) imagine themselves rotating the object 180 degrees along the surface (Rotate); or (4) identify and verbally rehearse the most prominent color of the object (Rehearse). The Function task required participants to retrieve information stored in long-term memory about the use of an object, whereas the Imagery task required participants to retrieve information about how to handle the object. The Rotate condition was devised as a control for the visual-spatial and movement-related demands of the Imagery task, and the Rehearse condition was devised as a control for the verbal demands of the Function task.

We posited that if left postMTG represents functions associated with objects, this region should be most active for the Function condition. In contrast, if this region represents action information, it should be most active for the Imagery condition. In fact, we found that left postMTG was engaged *specifically* when participants were asked to access function knowledge (Fig. 3–3*B*). These data indicate that postMTG represents semantic information about the function of an object, rather than how one interacts with it or how it typically moves when one uses it. In contrast to left postMTG, left inferior parietal lobule (IPL) [BA 40] (Fig. 3–3*C*) and dorsal premotor cortex (PMd) [BA 6]

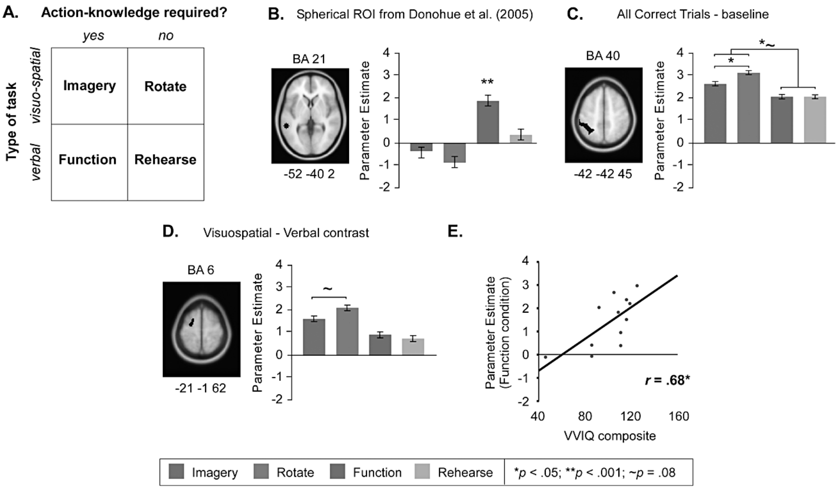

Figure 3–3 Brain regions associated with action representation with objects (Souza and Bunge, under review). *A.* The object study manipulated whether the action-knowledge was required and whether the task was primarily verbal or visual-spatial. *B.* A 6-mm spherical region-of-interest (ROI) was drawn, centered in the coordinates in left posterior middle temporal gyrus (postMTG; −56 −40 2) from Donohue et al. (2005). This ROI was *specifically* activated by the Function condition. *C.* Left inferior parietal (BA 40) activation was modulated by the task (visual-spatial > verbal) and in fact was greatest for Rotate. *D.* A similar pattern to that in left inferior parietal region was also found in left dorsal premotor cortex [BA 6]. *E.* Activation in left postMTG (BA 21) positively correlated with imagery ability as assessed by the Vividness of Visual Imagery Questionnaire (VVIQ) [Marks, 1973]. Note that VVIQ scores are reversed from the original scale such that higher scores reflect better visual imagery ability.

(Fig. 3–3*D*) were engaged more strongly in the Imagery than in the Function condition. Unlike PMd, ventral premotor cortex (PMv) [BA 6] was equally active across all four conditions. The roles of these regions in action representation are discussed further later.

Imagery and Semantic Retrieval: Two Routes to Retrieval of Object Knowledge

In this object knowledge study, we made an effort to direct participants to retrieve specific types of information associated with common household objects. Indeed, the fact that a number of brain regions were modulated by condition (and in opposite ways from other brain regions, in some cases) suggests that participants did tend to treat the conditions differently. In the real world, however, we most likely retrieve several types of information in parallel when we perceive a familiar object. Additionally, some individuals may tend to access one type of information more readily than another. In this study, we found that participants with better self-reported imagery ability—as measured by the

Vividness of Visual Imagery Questionnaire (VVIQ) [Marks, 1973]—engaged left postMTG more strongly when attempting to retrieve the function of an object (Fig. 3–3*E*), but not for the Motor Imagery, Rotate, or Rehearse conditions. Thus, participants may use visual imagery to assist in the retrieval of semantic knowledge about an object's function.

Action Representations in Premotor Cortex

Ventral Premotor Cortex

Similar to the postMTG, brain imaging studies of action knowledge have consistently reported activation in left PMv (BA 6/44) [for reviews, see Johnson-Frey, 2004; Kellenbach et al., 2003]. This region is active when subjects observe or copy movements, pretend to use tools, or generate verbs. As such, left PMv is believed to store movement representations, and to support the retrieval of motor information about tool use (Kellenbach et al., 2003).

In the road sign study described earlier (Donohue et al., 2005), the left PMv did not reflect rule knowledge, in that it was not more active for Correct than for Incorrect signs. However, PMv was significantly more active for Trained than for Old signs, and its response to Incorrect signs was intermediate to these (Fig. 3–4*A*). This finding was obtained regardless of the fact that subjects were not required to carry out any overt motor responses in the task. These results suggest that the PMv was engaged during attempts to retrieve action knowledge that does not come readily to mind. Additionally, as noted earlier with regard to the object knowledge study (Souza and Bunge, under review), PMv was engaged while participants considered pictures of artifacts—regardless of whether the type of information they were asked to retrieve about these artifacts was action-related (Fig. 3–4*B*). This result is consistent with the idea that PMv

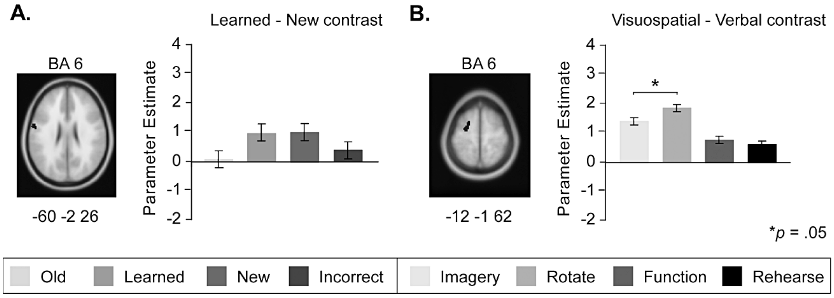

Figure 3–4 Involvement of premotor cortex in action knowledge. *A*. In the road sign study, a region of ventral premotor cortex (BA 6) showed maximal sensitivity to Learned (L) and New (N) signs, followed by Incorrect (I) and then Old (O) signs (Donohue et al., 2005). *B*. In the object study, we identified a cluster of dorsal premotor cortex activation (BA 6) that was significantly active for all conditions, but notably more so for the visual-spatial tasks (Souza and Bunge, under review).

is involved in the automatic retrieval of actions associated with manipulable objects (Kellenbach et al., 2003; Tranel et al., 2003; Johnson-Frey, 2004).

Dorsal Premotor Cortex

Left PMd (BA 6) is believed to support sensorimotor transformations (for reviews, see Picard and Strick, 2001; Chouinard and Paus, 2006). For example, it is active when participants are preparing to select between two movements relative to planning a single movement (Cavina-Pratesi et al., 2006). Lesion work shows that damage to PMd results in learning impairments for arbitrary sensorimotor associations in the monkey (Halsband and Passingham, 1982), as well as the human (Petrides, 1997). In the object knowledge study described earlier, we found that PMd activation was above baseline for all conditions, but was more active for the visuospatial tasks (Motor Imagery, Rotate > Function, Rehearse) [Fig. 3–4*B*], supporting the idea that this region aids in the planning of goal-directed movement.

Action Representations in Parietal Cortex

Another region that is often reported in the action knowledge literature is parietal cortex—in particular, the IPL and intraparietal sulcus (BA 40) [Johnson and Grafton, 2003; Johnson-Frey, 2004; Kellenbach et al., 2003]. Left IPL appears to be recruited only when subjects retrieve specific actions (Kellenbach et al., 2003), such as grasp-related movements associated with tools (Chao and Martin, 2000). This finding is consistent with the hypothesis that this region supports motor attention (Rushworth et al., 2001, 2003) and the literature on ideomotor apraxia indicating that patients with damage to this region have difficulty retrieving appropriate motor programs (Heilman et al., 1997).

In our initial rule study (Bunge et al., 2003), left IPL was sensitive to rule complexity during presentation of the instructional cue, as well as when subjects had to keep the rule in mind until they were prompted to select a response. In the object study, this region was most strongly modulated by the visual-spatial tasks, and in fact, was more active for Rotate than for Motor Imagery (Fig. 3–3*C*) [Souza and Bunge, under review], perhaps because participants could access familiar motor programs for the latter condition, but not for the former. Supporting a role in representing movements associated with objects, Motor Imagery–related activation in the left IPL was positively correlated with subsequent memory for having performed the imagery task on specific objects.

RETRIEVAL, SELECTION, AND MAINTENANCE OF RULE KNOWLEDGE

Studies Implicating VLPFC in Rule Learning and Rule Retrieval

Lesion studies in nonhuman primates demonstrate that VLPFC plays a critical role in rule learning and rule representation. VLPFC lesions in monkeys severely impair learning on conditional visual-motor tasks that require that they use one of several arbitrary stimulus-response (S-R) mappings to respond to a visual stimulus (Murray et al., 2000; Passingham et al., 2000) [see Chapter 7]. These lesions impair both the ability to use associations learned preoperatively and the ability to learn new associations rapidly within a single session (Bussey et al., 2002). VLPFC lesions in monkeys also lead to a deficit in learning a match-to-sample rule, indicating that VLPFC is important for learning complex rules as well as simple associations (Bussey et al., 2002).

Consistent with the lesion studies in nonhuman primates, neuroimaging studies in humans have also implicated VLPFC in rule representation (Toni et al., 1998; Toni and Passingham, 1999; Toni et al., 2001; Brass et al., 2003; Bunge et al., 2003; Brass and von Cramon, 2004). More broadly, VLPFC is believed to be important for active, or *controlled*, memory retrieval under situations in which relevant associations do not spring readily to mind (i.e., when relations between representations are weak, unstable, or ambiguous) [Petrides, 2002; see also Miller and Cohen, 2001]. Animal studies indicate that VLPFC retrieves information from the temporal lobes (Eacott and Gaffan, 1992; Petrides, 1996; Hasegawa et al., 1999; Miyashita and Hayashi, 2000). Indeed, disruption of the white matter tracts connecting VLPFC and ipsilateral temporal cortex leads to impaired visual-motor learning (Bussey et al., 2002; Parker and Gaffan, 1998). This and other findings support the hypothesis that VLPFC is involved in the effortful retrieval of rule knowledge (as well as other associations) from temporal cortex.

Engagement of VLPFC during Effortful Rule Retrieval

We previously postulated that VLPFC has an inverted U relationship with associative memory strength (Bunge et al., 2004). According to this hypothesis, VLPFC is recruited when subjects engage retrieval processes that lead to the successful recollection of knowledge, more so when the recollection is effortful (Wagner et al., 2001). However, under situations in which initial recollection attempts are unsuccessful and subjects abandon the retrieval effort, one might observe diminished reliance on VLPFC processes (Dobbins et al., 2003). Thus, the inverted U model predicts greatest activation in VLPFC during effortful recollection, intermediate levels during less effortful recollection, and the least activation when subjects abandon early retrieval attempts.

We found some support for the inverted U model in the road sign study, in that right VLPFC and right dorsolateral PFC (DLPFC)—like PMv (see Fig. 3–4*A*)—were most strongly engaged by recently Trained signs than by either Old or New signs (Donohue et al., 2005). In contrast to left postMTG, PFC was not sensitive to rule knowledge: It exhibited no differences in activation between signs whose meaning a subject knew and signs whose meaning he or she didn't know. These results suggest that the associations between road signs and the rules that they indicate are stored in postMTG, and that right VLPFC is engaged as needed to assist with rule retrieval.

In contrast to right VLPFC, left VLPFC did not show an inverted U pattern in the road sign study. Rather, this region was strongly engaged for all signs, regardless of knowledge or experience. This finding surprised us, because our earlier work had implicated left VLPFC in rule retrieval and maintenance (Bunge et al., 2003). We considered it likely that the unconstrained viewing paradigm used in the road sign study led subjects to actively attempt to interpret each sign as it appeared on the screen, thereby leading to equal activation of left VLPFC across conditions. However, we sought to further examine the role of left VLPFC in rule representation in a subsequent study, by testing whether it might be involved in selecting between sign meanings instead of or in addition to retrieving them. The rationale for this next experiment was based on a debate in the long-term memory literature as to whether left VLPFC plays a role in memory retrieval (Wagner et al., 2001) or in selection between active memoranda (Thompson-Schill et al., 1997).

Left VLPFC: Controlled Rule Retrieval, Rule Selection, or Both?

In the road sign meaning-selection study, we sought to test whether left VLPFC would be sensitive to rule retrieval demands or to rule selection demands (Souza et al., 2005). We used a two-factorial task design: (1) whether subjects were to retrieve a newly learned meaning for a sign or a meaning that they had learned years ago (New/Old), and (2) whether a sign had one or two possible meanings.

On "Old" trials, subjects were cued for the original meaning for a domestic sign with only one meaning. On "New" trials, subjects were cued for the meaning of a foreign sign, which they were trained on before scanning. On "Relearned-Old" trials, subjects were cued for the original meaning for a domestic sign with *two* meanings (the other meaning having been taught before scanning). On "Relearned-New" trials, subjects were cued for the *new* meaning for a domestic sign with two meanings. On each trial, a red or green border instructed subjects to retrieve either an Old or a New meaning. For signs with two meanings, this border was *critical* in determining the appropriate meaning to be remembered.

First, we tested whether left VLPFC (BA 45) was sensitive to controlled retrieval demands (New > Old; Relearned-New > Relearned-Old). As predicted, this region—identified from all correct trials relative to baseline—was more active for New than for Old signs; this finding supports the idea that left as well as right VLPFC are involved in the active retrieval of sign meanings (Fig. 3–5). However, contrary to prediction, left VLPFC was equally active on Relearned-New and Relearned-Old trials. This surprising finding is discussed later.

Second, we tested whether left VLPFC showed competition effects when subjects were forced to select between two possible rule meanings (Relearned-New > other signs) [Thompson-Schill et al., 1997; Badre et al., 2005]. Indeed, left VLPFC (BA 45) was engaged more strongly by Relearned-New than by Old signs (Fig. 3–5), which is, on the surface, consistent with a selection account of

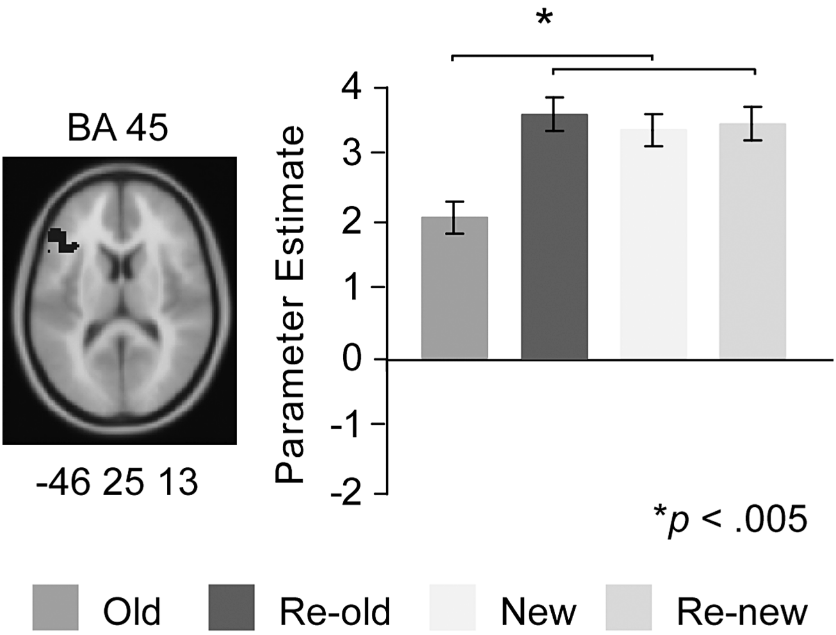

Figure 3–5 Left ventrolateral prefrontal cortex (VLPFC): controlled retrieval or response selection (Souza and Bunge, under review)? A region in left VLPFC (BA 45), extracted from a group contrast comparing all correct meaning retrievals relative to baseline, revealed that activation in this region was not wholly consistent with a controlled retrieval (Wagner et al., 2001) or a response selection (Thompson-Schill et al., 1997) account. O, Old; Re-Old, Relearned-Old; N, New; Re-New, Relearned-New.

VLPFC function. However, greater activation was not observed for Relearned-New than for New trials, which would be predicted by a selection account.

In effect, left VLPFC was more active on Relearned-New, Relearned-Old, and New trials than on Old trials, but did not distinguish between the first three conditions. These data would be consistent with a controlled retrieval account if it were the case that subjects tended to retrieve both meanings for signs with two meanings. By this account, subjects would retrieve a New sign meaning for all signs except for the Old ones, and this effortful retrieval process would engage VLPFC.

On the whole, these data are more consistent with a controlled retrieval account than with a selection account for left VLPFC (BA 45) involvement in this task. However, it is certainly the case that left VLPFC also plays a role in selecting between competing mental representations (Jonides et al., 1998; Nelson et al., 2003). Further, Badre and colleagues (2005) [see Chapter 16] found that, within left VLPFC, mid-VLPFC (BA 45) is involved in resolving competition and anterior VLPFC (BA 47) is involved in controlled semantic retrieval.

To address the issue of possible functional dissociations within left VLPFC in our second traffic study, we conducted region of interest (ROI) analyses based on the precise regions identified by Badre and colleagues. Anterior VLPFC (BA 47), a 6-mm sphere centered on Montreal Neurological Institute (MNI) coordinates −45 27 −15, was not engaged on the task relative to baseline. Thus, the retrieval of sign meanings may not rely on anterior VLPFC, a region associated with controlled semantic retrieval (Wagner et al., 2001; Badre et al., 2005). However, an ROI analysis of Badre's mid-VLPFC region (BA 45), a 6-mm sphere centered on MNI coordinates −45 27 −15 revealed the same interaction that we had previously observed with a larger ROI encompassing this region (Fig. 3–5). These and other findings suggest that mid-VLPFC may play a role in both the effortful retrieval of memory and the selection of relevant associations from among competing mnemonic representations.

VLPFC: Retrieval of Semantic Knowledge

In the object knowledge study discussed previously, subjects were asked to access semantic knowledge about an object (Function) or memory for the actions and movements associated with the use of the object (Imagery). The Rehearse and Rotate conditions were designed to control for verbal and visual-spatial task demands, respectively. Like postMTG, left VLPFC (BA 45) was activated by the following contrasts: Function > Rehearse and Function > Imagery (Fig. 3–6*A*). This finding is consistent with a large literature implicating left VLPFC in semantic memory (Vandenberghe et al., 1996; Gabrieli

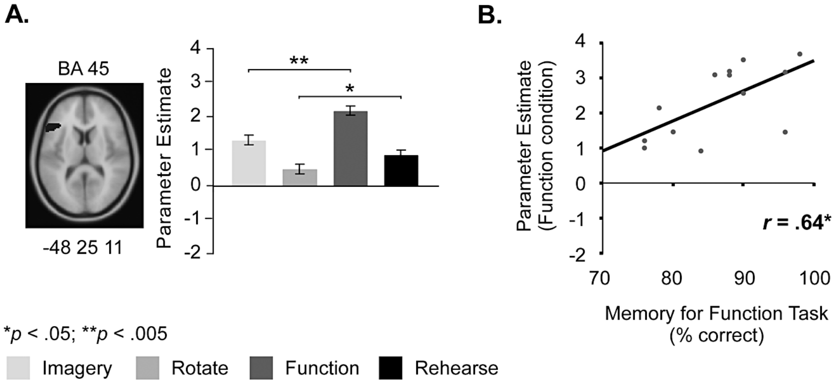

Figure 3–6 Left ventrolateral prefrontal cortex (VLPFC) and the retrieval of action knowledge (Souza and Bunge, under review). *A*. A region of left VLPFC (BA 45), identified from a group contrast sensitive to action knowledge (Imagery, Function >Rotate, Rehearse), showed the greatest response to the Function condition. *B*. The level of activation in left VLPFC for the Function condition correlated with later accuracy for the Function items of the post-test.

et al., 1998), and supports the hypothesis that VLPFC retrieves semantic information associated with objects from postMTG.

However, unlike postMTG, left VLPFC was more strongly engaged during imagery of object-specific actions (Imagery) than of actions that are not specifically associated with the objects (Rotate; see Fig. 3–6*A*). Thus, left VLPFC activation reflected retrieval of *both* functions and actions associated with objects. This region likely accesses multiple types of information from distinct brain regions, including object functions and rules from postMTG and information about how to interact with an object from parietal or premotor cortex. Collectively, these inputs provide contextual information that can inform the selection of goal-relevant and contextually appropriate actions.

VLPFC Activation Correlated with Subsequent Memory Performance

In the object knowledge study, subjects were given an incidental memory test after the scan session, in which they were asked to indicate which task they had performed on each of a series of objects (Imagery versus Function). Left VLPFC activation on the Function task was correlated with subsequent memory for thinking about the function of a specific object (Fig. 3–6*B*). In contrast, a correlation was not observed between VLPFC activation on the Imagery task and subsequent memory. Thus, although left VLPFC is active during performance of the Imagery task (albeit to a lesser extent than during the Function task), its engagement appears not to be necessary for later memory of this mental operation. Unlike VLPFC, postMTG, parietal, and premotor regions did not exhibit subsequent memory effects.

This finding is broadly consistent with earlier findings that greater engagement of left VLPFC during word encoding is associated with greater subsequent episodic memory for the presentation of those words (Wagner et al., 1998, 1999; Kirchhoff et al., 2000). These findings provide new insight into the role of VLPFC in rule learning: VLPFC can assist with rule learning by helping to retrieve not only specific associations with a stimulus (be it a real-world object or a symbol), but also memories for the *context* in which one had seen the stimulus previously, and how one had responded to the stimulus then.

Distinct Neural Representation for Different Types of Rules?

Neuroimaging studies in humans and electrophysiological recordings in nonhuman primates implicate both VLPFC and mid-DLPFC (BA 9, 46) in rule representation (for review, see Bunge, 2004). However, as noted earlier, neuropsychological studies in nonhuman primates implicate VLPFC, but not DLPFC, in rule representation. Damage to DLPFC causes little or no impairment on visual-motor conditional tasks in either humans or nonhuman primates (see Murray et al., 2000), with the exception of posterior DLPFC in humans (BA 8) [Petrides, 1997; Amiez et al., 2006; Monchi et al., 2006]. These apparent discrepancies raise two possibilities: (1) mid-DLPFC represents some types of rules, but not others; and (2) DLPFC is engaged during rule representation without being *required* for adequate task performance.

In considering the types of rules that DLPFC may represent, two possibilities are suggested by the extant literature. First, DLPFC may be important for representing rules that require overriding a prepotent response tendency. Indeed, one study showed sustained mid-DLPFC (BA 9) activation while participants prepared to perform the Stroop task (MacDonald et al., 2000), and another showed that DLPFC (but not VLPFC) was more active when subjects were able to prepare to withhold a response on a go/no-go task than when they received no advance warning (Hester et al., 2004). Instead or additionally, DLPFC may not be engaged for low-level rules, such as stimulus-response associations, but may be recruited for more complex rules. Such a finding would be consistent with the hypothesis that DLPFC is recruited as needed to manage, monitor, or manipulate information kept active by VLPFC (D'Esposito et al., 1999; Rypma et al., 1999; Bor and Owen, 2006).

Our laboratory designed an experiment to test the hypothesis that VLPFC and DLPFC contribute differentially to rule representation (Donohue et al., under review). More generally, the aim of the second rules study was to investigate whether rules of different kinds are maintained differentially in the brain. To this end, participants performed two distinct tasks, at different levels of difficulty, during acquisition of event-related fMRI data. On each trial, an instructional cue appeared briefly on the screen, followed by a delay and a probe, during which a response occurred (Fig. 3–7*A*; see color insert). In the Stroop task, named after the classic test from which it was adapted, participants were cued to determine either the ink color or the color name associated with a word stimulus. The Ink condition was more challenging than the Word condition, because it involved overriding the automatic tendency to focus on the word's meaning. In the Memory task, participants were tested on their memory for pairs of color words learned before scanning. Participants had to retrieve four word pairs from long-term memory for each of two instructional cues (set A or set B; High memory load), and had to retrieve one word pair for each of two additional cues (set C or set D; Low memory load; Fig. 3–7*B*).

The more difficult condition in the Stroop task (Ink versus Word) involved suppression of response competition. However, in the Memory task, the more difficult condition (High load versus Low load) placed greater demands on long-term memory retrieval and working memory maintenance. Thus, we were able to test whether different regions in lateral PFC were modulated by response competition demands and memory demands during rule maintenance. We predicted that left VLPFC would be generally involved in rule representation, whereas DLPFC would specifically assist in the representation of inhibitory or complex rules.

As predicted, left VLPFC (BA 44/45) was engaged during the maintenance of all four types of rules, consistent with a general role in rule representation (Fig. 3–7*C, top*). This region was most strongly engaged by the High load. This finding extends the verbal working memory literature by showing

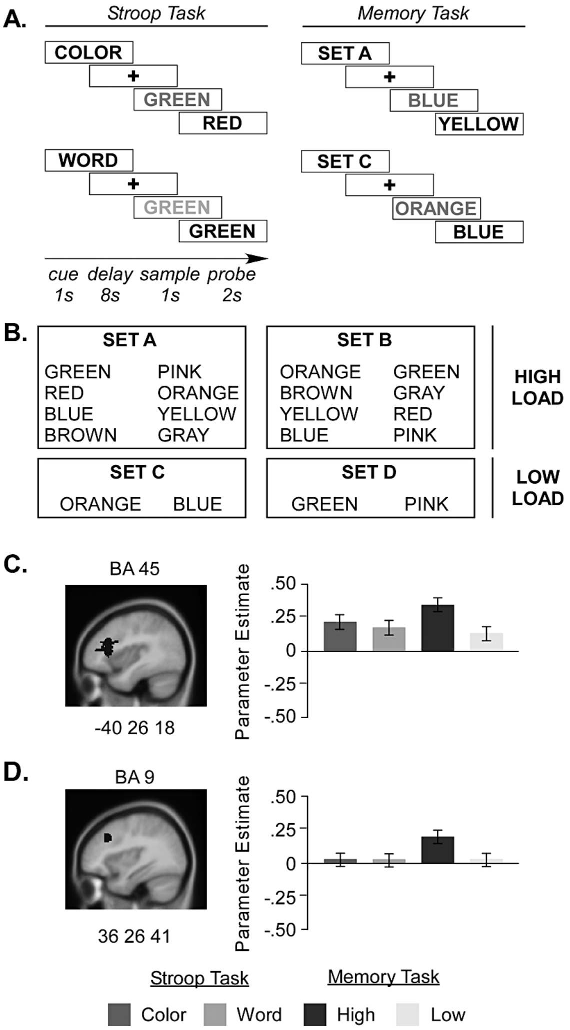

Figure 3–7 Retrieving and maintaining different rule types for future action (Donohue et al., under review). *A*. In the second rules study, participants memorized various set sizes of color pairings. *B*. On a given trial, a cue would indicate the type of rule to be followed. The delay was followed by a sample and a probe, and participants responded to the sample-probe pairing based on the instructional cue. *C*. During the Delay period, left ventrolateral prefrontal cortex (BA 45) was significantly activated for every condition. *D*. Right dorsolateral prefrontal cortex (BA 9), however, was specifically activated for the High-load condition.

load-dependent *rule* maintenance in VLPFC, in addition to load-dependent maintenance of other types of representations (see also Bunge et al., 2003). A homologous region in right VLPFC showed the same pattern, but was not as robustly engaged. In contrast to VLPFC, right DLPFC (BA 9; middle frontal gyrus [MFG]) was specifically engaged during the delay period for the maintenance of the High load rule (Fig. 3–7*C*, *bottom*). These findings are consistent with the prediction that DLPFC is not as generally involved in rule maintenance as VLPFC.

No region was preferentially engaged by the Ink condition during the delay period, suggesting that inhibitory rules are maintained online in a similar fashion to non-inhibitory rules. Conscious rule maintenance appears to rely on neural circuitry associated with verbal working memory, suggesting that rules do not enjoy special status relative to other types of information held online.

However, during the cue and probe periods, several control-related brain regions showed transient responses specifically for the Ink instruction, including right DLPFC (BA 9, MFG, inferior to the previous right DLPFC ROI) as well as right VLPFC, a region that has been implicated in response inhibition

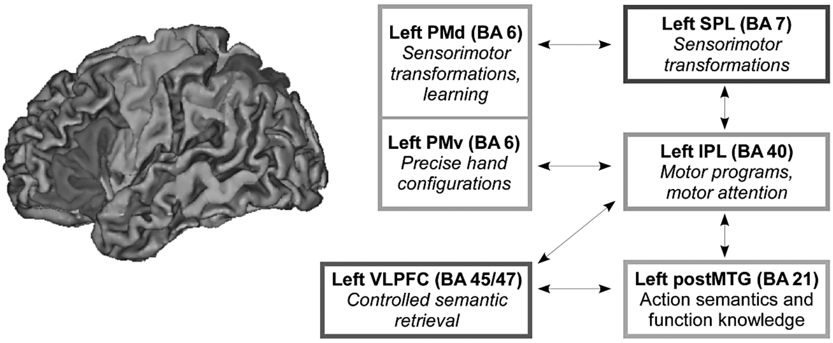

Figure 3–8 A theoretical framework for brain regions involved in action representation. Left ventrolateral prefrontal cortex (VLPFC) [BA 44/45/47] is involved in the controlled retrieval of semantics and rules (Wagner et al., 2001; Bunge et al., 2003). Left posterior middle temporal gyrus (postMTG) [BA 21] is involved in representing rules and action semantics (Bunge et al., 2003; Donohue et al., 2005; Souza and Bunge, under review). Ventral premotor cortex (PMv) [BA 6] is involved in precise hand grips required for object-related interactions (Kellenbach et al., 2003). Dorsal premotor cortex (PMd) [BA 6] is involved in sensorimotor learning and transformations (Petrides, 1997). Inferior parietal lobule (IPL) [BA 40] is involved in motor programs (Chao and Martin, 2000; Kellenbach et al., 2003) and motor attention (Rushworth et al., 2001, 2003). Superior parietal lobule (SPL) [BA 7] is involved in goal-directed sensorimotor transformations (Fogassi and Luppino, 2005). Left hemisphere fiducial rendering is from Caret 5.5 (Van Essen et al., 2001, 2002; http://brainmap.wustl.edu/caret). Regional demarkations are imprecise, and are meant for illustrative purposes only; the region encompassing the premotor cortex includes the primary motor cortex.

(Konishi et al., 1999; Garavan et al., 1999; Bunge et al., 2002; Aron et al., 2003). Thus, as predicted, two different types of rules were represented differentially in the brain—at least during rule retrieval and implementation, if not during maintenance.

Bunge and Zelazo previously hypothesized further neural dissociations in PFC with respect to rule representation (Bunge and Zelazo, 2006) [see Chapter 19]. According to this framework, orbitofrontal cortex represents values associated with specific stimuli or choices (see Chapter 2), whereas lateral PFC represents specific sets of response contingencies. Inspired by Kalina Christoff's model of prefrontal organization (Christoff and Gabrieli, 2002), we posited a hierarchy of rules represented in lateral PFC. Our framework posits that all manner of rules are represented in VLPFC and that rules of increasing structural complexity additionally rely on DLPFC or anterior PFC (BA 10). These proposed dissociations within PFC have yet to be tested explicitly. We have used this framework as a theoretical account of developmental improvements in rule use over childhood; the development of rule use is discussed further in Chapter 19.

CONCLUSION

We have focused here on several components of the neural mechanisms involved in rule representation (Fig. 3–8; see color insert). Extant data suggest that: (1) postMTG stores semantic knowledge associated with cues in the environment; (2) various regions in parietal and premotor cortices represent actions at different levels of abstraction; and (3) VLPFC is involved in controlled rule retrieval and conscious rule maintenance. Additionally, PFC subregions, including DLPFC and anterior PFC (not shown in Fig. 3–8), are involved in rule representation as needed, depending on the kind of rule. Indeed, rules can be actively maintained in verbal working memory, with the degree of engagement of lateral PFC depending on the amount of information to be held in mind. Future research on the neural mechanisms underlying rule retrieval, maintenance, and implementation will necessarily rely on brain imaging measures with higher temporal resolution than the blood-oxygen-level dependent (BOLD) signal measured with fMRI.

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