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Inferior Frontal and Middle Temporal Lobe Contributions to Goal-directed Cognition

by

Michael James Souza

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

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in the

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of the

University of California, Berkeley

Committee in charge:

Professor Silvia A. Bunge, Chair

Professor Richard B. Ivry

Professor Arthur P. Shimamura

Professor Michael A. Silver

Professor Anthony J-W Chen

Spring 2010

Abstract

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by

Michael James Souza

Doctor of Philosophy in Psychology

University of California, Berkeley

Professor Silvia A. Bunge, Chair

The ability to utilize stored semantic knowledge in the service of goal-directed behavior is an important component of cognitive control. Though a growing amount of work has been done to characterize the precise role of ventrolateral prefrontal cortex (VLPFC) in memory processing, it is currently unclear whether left VLPFC supports controlled access to long-term memory and/or post-retrieval selection to stimuli outside of the explicitly verbal domain. Furthermore, the precise contribution of left posterior middle temporal gyrus (left pMTG) in supporting goal-relevant knowledge is unclear. More specifically, it is uncertain whether this region represents semantic function knowledge about a stimulus and/or knowledge about how a stimulus moves when it is in motion. The goal of this volume is to further explore the contributions of left VLPFC and left pMTG in accessing and representing goal-relevant knowledge, respectively. Chapter 1 reviews the literature on the involvement of PFC in goal-directed cognition and mnemonic processing, as well as the evidence supporting the role of left pMTG in representing knowledge. Chapter 2 discusses a functional MRI study examining the neural correlates of controlled retrieval and selection using foreign and domestic traffic signs. The results suggest that the anterior portion of left VLPFC is more sensitive to controlled retrieval, the posterior extent is more sensitive to selection demands, and the region intermediate to these two is sensitive to both demands. Chapter 3 describes an fMRI study focusing on the retrieval of distinct types of knowledge relevant to everyday manipulable objects. We found that left anterior VLPFC was driven by semantic retrieval demands, and that a region in left pMTG, previously associated with correctly retrieving the meanings to traffic signs, was most engaged when accessing knowledge about the object's function. To control for other factors (e.g., task difficulty) which may have fueled these results, we replicated this study while better controlling for task demands and difficulty (Chapter 4). In Chapter 5, these findings are synthesized and future directions are discussed. In summary, this work supports the involvement of left VLPFC and left pMTG in the retrieval and representation of stored knowledge that informs our actions.

Dedication

To my wife, Hannah

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Chapter 1

When we set a goal such as searching out a job that suits our qualifications, exploring ways to improve our health and well-being, or even figuring a way to finance our child's college education, we are setting up a complex, multi-step goal that requires a fair amount of planning, attention and persistence to be successfully accomplished. In pursuing these goals and others like them, we require the ability to keep our goal(s) in mind, to effectively manage goal-irrelevant distractions, to retrieve goal-relevant knowledge from long-term memory, to monitor whether our current behavior is consistent with our goals, and to flexibly modify our behavior in the face of ever-changing circumstances. Cognitive abilities that enable flexible, goal-directed behavior, such as those described above, are known as “executive functions” or components of “cognitive control.” These processes constitute an essential component of human cognition and as such, they have received a great deal of attention in recent years.

Cognitive scientists have been working for many years to characterize the set of functions associated with the control system. In 1974, Baddeley & Hitch published a theory of working memory (WM) which posited that control was vested in a structure called the “Central Executive,” which allocates cognitive resources to visual and auditory subsystems. Another model proposed by Norman and Shallice is known as the “Supervisory Attentional System” (SAS; Norman and Shallice, 1986). The SAS was theorized to be involved in guiding our behavior in a number of instances, such as when our behavior would benefit from planning and organization, or when a pre-potent response was no longer appropriate, as is the case in the Stroop task. Though these and other theories were thoughtfully crafted, at the time, it was not yet technologically possible to search for the control module *in vivo* in the human brain.

With the advent and rapidly increasing use of neuroimaging technologies such as positron emission tomography (PET) in the 1980's and functional magnetic resonance imaging (fMRI) in the early 1990's, neuroscientists became able to constrain theories of cognition with studies of brain function. Early work from neuroimaging and work with non-human primates began to converge on the hypothesis that prefrontal cortex (PFC), which constitutes nearly one-third of the human cortex and is one of the cortical regions that has undergone the most evolutionary development (Fuster, 2001), is a particularly important node for control processes. In the following section, I will review why PFC is considered a strong candidate site for supporting cognitive control, pulling evidence from neuroimaging, neurophysiology, and neuropsychology.

Cognitive Control & PFC

According to Miller and Cohen (2001), for a brain region to be able to intelligently exert control over other regions, it should satisfy a number of important requirements. It must be able to (1) maintain goal-relevant information in the face of distraction while also being able to update goals and information when necessary, (2) access and influence information processing in other regions, and (3) flexibly modify goals and behaviors as the context of our actions changes. Indeed, there is good evidence from a number of lines of work that PFC satisfies all of these fundamental requirements.

First of all, PFC has been strongly linked to maintaining goal-relevant information and resisting goal-irrelevant information. Functional neuroimaging studies have shown that lateral PFC is involved in the maintenance and manipulation of goal-relevant information in working memory (D'Esposito et al., 1998; D'Esposito & Postle, 1999; D'Esposito, Ballard, Postle & Lease, 1999; Rypma & D'Esposito, 1999), as well as the successful resolution of interference (Nelson, Reuter-Lorenz, Sylvester, Jonides & Smith, 2003; Nee, Jonides & Berman, 2007; Persson, Welsh, Jonides & Reuter-Lorenz, 2007). Consistent with these neuroimaging findings, recent work using pattern classification of activity in inferior PFC during the maintenance of goal-relevant rules has been shown to be strongly predictive of which task rule a participant will use to guide their actions (Bode & Haynes, 2009).

Other approaches also corroborate the neuroimaging findings. Neurophysiological work with non-human primates has demonstrated that PFC neurons are indeed able to represent abstract goal information in a manner independent of the physical properties of task stimuli (Wallis, Anderson & Miller, 2001). Neurochemically, depletion of the neurotransmitter dopamine, which is thought to amplify the signal-to-noise ratio for task-relevant knowledge (Foote & Morrison, 1987), has been shown to produce severe impairments on a spatial delay task that are almost as pronounced as what would result from a PFC lesion (Brozoski, Brown, Rosvold & Goldman, 1979). Likewise, temperature cooling of the PFC, which reduces neural activity, results in comparable performance impairments (Bauer & Fuster, 1976). Finally, patients with damage to PFC may manifest a number of goal-directed impairments, such as increased distractibility (Chao & Knight, 1998; Thompson-Schill et al, 2002), "goal neglect," which refers to a functional disconnect between goal knowledge and observable behavior (Duncan et al., 1996), and "utilization behavior," where individuals maintain an extreme reliance on environmental cues, rather than internal goals, to guide their actions (Lhermitte, 1983; Shallice, Burgess, Schon & Baxter, 1989). In summary, converging evidence strongly supports the involvement of PFC in maintaining goals and goal-relevant information.

Second, PFC receives extensive knowledge about its external environment and is capable of biasing processing in other regions. Although no primary sensory cortices exist in the frontal lobes, PFC is fed highly processed sensory information from posterior cortices. As described by Fuster (2000), PFC sits atop the "Perception-Action Hierarchy," which refers to the fact that it receives highly processed polymodal inputs and is able to bias motor commands thanks to its prime location adjacent to cortical motor areas. PFC also maintains extensive connectivity to many other cortical and sub-cortical regions (for review, Barbas, 2006), and coupled with extensive intraconnectivity within PFC, it is clear that PFC is well-positioned to exert informed control. Consistent with this notion, a growing body of work in functional neuroimaging is providing supported this view. For example, work from Adam Gazzaley and colleagues has suggested that goal-driven enhancement and suppression signals emanating from PFC modulate responses to face and scene stimuli in the fusiform face area (FFA) and parahippocampal place area (PPA), respectively (Gazzaley, Cooney, McEvoy, Knight & D'Esposito, 2005; Gazzaley, Cooney, Rissman & D'Esposito, 2005). Though neuroimaging work like this is not able to prove a causal link between PFC and posterior processing areas, as it is a correlational method, it has laid the foundation for other researchers to further scrutinize this potential functional link. Taken

together, PFC's extensive connectivity and a growing body of evidence supports the notion that it is able to bias processing in a manner that supports goal-directed behavior.

Finally, there is good evidence that PFC is capable of flexibly modifying goals and behaviors when necessary. Dorsolateral prefrontal cortex (DLPFC) has been associated with exerting control to override pre-potent responses, as is the case with stimulus conflict in the Stroop task (Carter et al., 1998; Botvinick, Nystrom, Fissell, Carter & Cohen, 1999). Also, recent work in task switching suggests that the inferior frontal junction (IFJ) is particularly important for maintaining and updating task sets (for review, Derrfuss, Brass, Neumann & von Cramon, 2005). Finally, evidence from neuropsychology has long demonstrated that PFC patients have compromised cognitive flexibility. This impaired flexibility, which is known as "perseverative behavior," is characterized by repeating previously relevant behaviors that are no longer currently relevant. This behavior is classically elicited by neurologists when employing the Luria 3-step motor test, where perseverative patients tend to repeat a single move multiple times rather than properly following the sequence. In the experimental setting, researchers have extensively used the Wisconsin Card Sorting Task (WCST) to identify perseverative behaviors. In the WCST, patients are able to initially learn sorting rules but they have an inordinate amount of difficulty when the rules are switched (Stuss et al., 2000). In sum, PFC appears to be critical for flexibly adjusting our behavior when the circumstances dictate it.

In a departure from initial models which suggested that control may emanate from one central brain structure, as was implicitly suggested in the CES and SAS, researchers have worked intensely to map out the specific cognitive functions of all sub-regions of PFC. In particular, one sub-region that has received a great deal of attention is ventrolateral prefrontal cortex (VLPFC; Brodmann's area [BA] 44, 45, 47). In the following section, I will describe work examining the role of VLPFC, which has been associated with rule representation and semantic processing.

Rule knowledge, semantic processing and VLPFC

Work from a number of approaches, including neuroimaging and neurophysiology, has strongly suggested that VLPFC plays an important role in acquiring and later retrieving rules to guide behavior from long-term memory (Bunge, 2004; Bunge, Wallis, Parker, Brass, Crone et al., 2005; Bussey, Wise & Murray, 2001; Murray et al., 2000; Passingham et al., 2000). Indeed, work from our laboratory has supported this hypothesis, particularly for left VLPFC (e.g., Bunge, Kahn, Wallis, Miller & Wagner, 2003; Crone, Wendelken, Donohue & Bunge, 2006; Donohue, Wendelken & Bunge, 2008). Thus, VLPFC appears to be an important region for learning and implementing the "rules of the game" (Miller & Cohen, 2001).

Neuroimaging work in humans also supports the hypothesis that left VLPFC is involved in semantic encoding and retrieval (Badre and Wagner, 2002; Demb, Desmond, Wagner, Vaidya, Glover et al., 1995; Gabrieli et al., 1998; Poldrack, Wagner, Prull, Desmond, Glover et al., 1999; Wagner, Pare-Blagoev, Clark & Poldrack, 2001). However, the precise contribution of left VLPFC in semantic processing is not entirely clear. One idea regarding left VLPFC function, known as the controlled retrieval hypothesis, contends that this region guides non-automatic access to goal-relevant semantic knowledge (Goldberg, Perfetti, Fiez & Schneider, 2007; Wagner, Desmond, Demb, Glover & Gabrieli, 1997; Wagner et al., 2001). An alternative idea,

known as the selection hypothesis, maintains that left VLPFC selects goal-relevant information from multiple active, competing representations (Kan, Kable, Van Scoyoc, Chatterjee & Thompson-Schill, 2006; Kan & Thompson-Schill, 2004; Persson, Sylvester, Nelson, Welsh, Jonides et al., 2004; Thompson-Schill, D'Esposito, Aguirre & Farah, 1997; Thompson-Schill et al., 1999). Resolution of this debate has proved to be particularly challenging because in many cases, manipulations of controlled retrieval are confounded with changes in selection demands (Thompson-Schill, Bedny & Goldberg, 2005). Even worse, some have suggested that much of the work on this issue uses fundamentally flawed manipulations of controlled retrieval and selection (Synder & Munakata, 2008). In addition to these limitations, it is important to note that most of these studies use verbal stimuli. Thus, far less is known about how left VLPFC is involved in paradigms involving non-verbal stimuli and/or no overt response requirements.

In the cognitive control literature, considerably more focus is dedicated to how PFC guides access to goal-relevant knowledge, with far less focus on the locus of these representations. In the following section, I will describe previous work examining the role of the temporal lobes in representing long-term knowledge.

Knowledge representation and the temporal lobes

There is growing evidence that the left posterior temporal lobe plays an important role in supporting rule knowledge. Early work from our laboratory showed that correctly retrieving behavioral rules from long-term memory, such as the fact that a pronounceable non-word is associated with a directional button press, was sufficient to engage the left posterior middle temporal gyrus (pMTG; BA 21; Bunge et al., 2003). In a follow-up study, we showed that correctly retrieving the meaning to well-known and newly-learned road signs also engaged this same region in left pMTG (Donohue et al, 2005), suggesting that it may be involved more generally in representing functional semantics associated with visual stimuli (Bunge, 2004).

Interestingly, activation in this vicinity of left pMTG is also frequently observed in studies involving manipulable objects (for reviews, see Martin & Chao, 2001; Johnson-Frey, 2004; Lewis, 2006). Given this region's proximity to regions that process visual and biological motion, it has been argued that it might play a role in supporting "action knowledge," or features of motion, associated with objects (Martin & Chao, 2001). Thus, it is unclear whether left pMTG supports the representation of functional semantics and/or action knowledge associated with the use of these and other visual stimuli.

The present work

The current research seeks to address and clarify two points about the contribution of left VLPFC and left pMTG to goal-directed cognition. First, how do anterior and posterior VLPFC, which have been associated with controlled retrieval and selection, respectively, contribute to processing knowledge about nonverbal stimuli in the absence of overt responses? Given that much of the work on controlled retrieval and selection uses verbal stimuli, this aim seeks to better generalize our understanding of how left VLPFC processes a wider variety of information. Second, what is the precise contribution of left pMTG in representing knowledge? A more precise understanding of how left pMTG supports knowledge representation would constitute an important advancement in how this region contributes to goal-directed behavior.

Chapter 2

When deciding on a course of action, we often rely on previously learned rules, or prescribed guides for behavior (Merriam-Webster Dictionary, 1974). In recent years, neuroscientists have begun to explore the neural underpinnings of rule-guided behavior (Bunge and Wallis, 2008; Murray, Bussey & Wise, 2000; Passingham, Toni & Rushworth, 2000). Neurophysiological and human neuroimaging studies have revealed that lateral prefrontal cortex (PFC) plays an important role in the learning and subsequent retrieval of rules from long-term memory. In particular, ventrolateral PFC (VLPFC; Brodmann's area [BA] 44, 45, 47) has been strongly implicated in rule representation (Bunge, 2004; Bunge, Wallis, Parker, Brass, Crone et al., 2005; Bussey, Wise & Murray, 2001; Murray et al., 2000; Passingham et al., 2000). Indeed, in non-human primates, lesions to VLPFC or disruption of the connections between VLPFC and ipsilateral inferotemporal cortex result in performance impairments in rule learning and utilization (Bussey, Wise & Murray, 2002; Murray et al., 2000). Further, neuroimaging data show that left – and to a lesser extent right – VLPFC is active during rule retrieval, maintenance, and implementation, in a manner that is sensitive to rule complexity (e.g., Bunge, Kahn, Wallis, Miller & Wagner, 2003; Crone, Wendelken, Donohue & Bunge, 2006; Donohue, Wendelken & Bunge, 2008).

In humans, it is well-known that left VLPFC plays a critical role in language production and comprehension (Gabrieli, Poldrack & Desmond, 1998). Thus, it is tempting to conclude that rules engage left VLPFC only because we tend to represent rules verbally. However, VLPFC is critical for rule representation even in non-human primates, who are largely devoid of linguistic capacity. VLPFC has strong associations with temporal cortex, and is therefore well-placed to assist in the retrieval of information stored therein (Petrides, 1996).

The literature on long-term memory in humans indicates that left VLPFC is involved in semantic encoding and retrieval (Badre and Wagner, 2002; Demb, Desmond, Wagner, Vaidya, Glover et al., 1995; Gabrieli et al., 1998; Poldrack, Wagner, Prull, Desmond, Glover et al., 1999; Wagner, Pare-Blagoev, Clark & Poldrack, 2001). One idea regarding left VLPFC function, known as the controlled retrieval hypothesis, argues that this region is important for guiding access to goal-relevant semantic knowledge (Goldberg, Perfetti, Fiez & Schneider, 2007; Wagner, Desmond, Demb, Glover & Gabrieli, 1997; Wagner et al., 2001). An alternative idea, known as the selection hypothesis, contends that the role of left VLPFC is to select goal-relevant information from competing representations (Kan, Kable, Van Scoyoc, Chatterjee & Thompson-Schill, 2006; Kan & Thompson-Schill, 2004; Persson, Sylvester, Nelson, Welsh, Jonides et al., 2004; Thompson-Schill, D'Esposito, Aguirre & Farah, 1997; Thompson-Schill et al., 1999). Though in some cases manipulations of controlled retrieval can be bound to changes in selection (for discussion, Thompson-Schill, Bedny & Goldberg, 2005), it is possible to manipulate controlled retrieval and selection demands separately, as selection is thought to operate post-retrieval (for review, Badre & Wagner, 2002).

Using a paradigm with materials modified from Wagner and colleagues (Wagner et al., 2001), Badre used factor analysis to examine whether controlled retrieval and selection can be reduced to one putative cognitive process (Badre, Poldrack, Pare-Blagoev, Insler & Wagner, 2005).

Analysis of their behavioral and fMRI data supported a distinction between controlled retrieval and selection, with the former moderated by left anterior VLPFC (aVLPFC; BA 47/11), and the latter by mid-VLPFC (BA 44/45) and, to a lesser extent, posterior VLPFC (pVLPFC; BA 44/6). Many of the aforementioned studies involved variants of a task in which participants must select a response from among a set of words. In this study, we sought to test whether prior findings regarding the role of these left VLPFC subregions in controlled retrieval and selection would extend to a very different paradigm involving non-verbal stimuli and no overt response requirements.

Thus far, the majority of neuroscientific studies on rule representation have involved stimuli that have been arbitrarily associated with a task rule in the laboratory, immediately prior to testing. To examine how experience modulates rule-related activation in left VLPFC and temporal cortex for non-verbal stimuli, our group previously conducted a functional magnetic resonance imaging (fMRI) study in which participants retrieved the meanings to road signs that they had known for years ('Old'), learned immediately prior to testing ('New'), or never learned ('Untrained') (Donohue, Wendelken, Crone & Bunge, 2005). We found that a large swath of left VLPFC (BA 44, 45, 47) activation was strongly and indiscriminately engaged across these three conditions. In contrast to left VLPFC, right VLPFC (BA 47/11) was sensitive to retrieval demands (New > Old), consistent with our prior work (Bunge, Burrow & Wagner, 2004). Finally, left posterior middle temporal gyrus (pMTG; BA 21) was exclusively active when participants were retrieving a sign meaning they learned prior to test (Old, New > Untrained), consistent with a role in representing rule knowledge.

The finding that left VLPFC was not modulated by controlled retrieval demands (Donohue et al., 2005) was unexpected, given the prior studies indicating that this region plays a key role in representing task rules (see Bunge, 2004). We tentatively concluded that this region was indiscriminately engaged as participants attempted to interpret the signs presented to them in this open-ended task. The lack of an effect of New > Old may have been accounted for by the fact that participants were explicitly told the meanings of the New signs, but not the Old signs, prior to testing; this aspect of the task design may have served to reduce the differences in controlled retrieval demands between the conditions.

In an attempt to further probe the role of left VLPFC in rule-guided behavior, the present study manipulated both controlled retrieval and selection demands in a task adapted from our prior study (Donohue et al., 2005). Participants encountered four conditions: 'Old' meanings were domestic road signs with their corresponding meaning; 'New' meanings were never-before learned foreign road signs in which participants were taught the appropriate meaning; 'Re-Old' meanings were the original meanings to a different set of domestic road signs, and 'Re-New' meanings were new, arbitrary second meanings associated with the signs presented in the Re-Old condition. Participants were explicitly given the meanings of all signs during the study phase. At test, during fMRI data acquisition, a red or green border cued participants to retrieve either a new or old sign meaning. For the signs with two meanings, this cue was needed to determine which meaning to focus on; for the familiar or newly learned signs with only one meaning, this cue was largely redundant, but was included to maximize comparability between conditions.

This design allowed us to manipulate controlled retrieval and selection demands separately, and to test the role of left and right VLPFC in retrieval and selection with respect to non-verbal stimuli. Specifically, we sought to test whether anterior VLPFC (BA 47) is primarily driven by controlled retrieval demands, and the more posterior extent of VLPFC (BA 44/45) by selection demands.

Although our primary goal was to characterize the activation profile of VLPFC in this task, we also sought to examine the activation profile in left pMTG (BA 21). We predicted that left pMTG would be insensitive to New > Old signs (Donohue et al., 2005), but that this region might be more active during the viewing of signs with two meanings, given prior evidence that this region is more active when more information is retrieved (Badre et al., 2005).

Methods

Participants

Seventeen healthy, right-handed volunteers were recruited from the University of California, Davis, and greater Sacramento area, and all were financially compensated for their participation. The success of the selection manipulation hinged on participants' ability to remember both meanings associated with a given sign. In light of this consideration, four of the participants were excluded on the basis of poor memory for sign meanings (< 70% correct on any of the four road sign conditions as measured in a post-scan test). As such, thirteen participants (6 male; 18-30 years old, $M=23.1$) were included in the study.

Given that the task required knowledge of the meanings of road signs, we recruited participants who possessed valid U.S. Driver's Licenses, and had been driving for a minimum of one year (range of driving experience: 1.5-14.3 years, $M=6.9$). Because of the large range of driving experience in the group, we examined whether driving experience correlated with overall performance on the task. This analysis revealed a non-significant negative correlation, $r=-0.17$, $p=.59$, indicating that amount of driving experience did not affect task performance. Although 12 of the 13 participants included in the study had traveled outside the United States, only three had ever driven while abroad; as such, we expected that these participants would be largely unfamiliar with the meanings of foreign road signs introduced in the experiment. Informed consent was obtained from all participants, and study procedures were approved by the Institutional Review Board at UC Davis.

Stimuli

A total of 90 images of road signs from the United States (i.e. 'domestic') and 45 images of foreign road signs were included in the study. The foreign road signs originated from a number of countries, and were selected on the basis that they did not closely resemble any common U.S. signs. Where possible, signs that did not contain any text were selected for the experiment; for signs containing text, the wording was blurred so that participants would be unable to read them. The blurring was done in such a way as to simulate the way in which text on a sign might appear from a distance (Donohue et al., 2005).

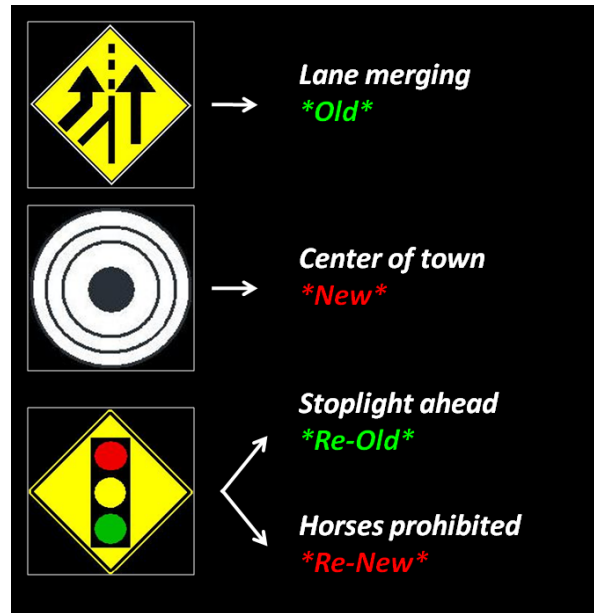


Figure 2.1. Experimental conditions. The present study manipulated controlled retrieval and selection demands by varying when a sign meaning was learned (old, new) and how many meanings a sign possessed (one, two). “Old” referred to domestic signs with their original meaning, “New” referred to foreign road signs which participants learned the meaning of, “Re-Old” referred to the original meaning of a domestic sign that has two possible meanings, and “Re-New” referred to newly learned, second possible meaning for a domestic sign. During fMRI scanning and the post-scan test, each sign was surrounded by a colored border to indicate which sign meaning they should consider (only important for signs with two meanings). Old and Re-Old meanings were always indicated by a green border, and New and Re-New meanings were always indicated by a red border (as indicated by the color of the condition names in this figure). In the experiment, all signs were presented in full color.

The task included four conditions: Old, New, Re-Old, and Re-New (Figure 1). Old stimuli consisted of 45 randomly selected domestic road signs whose correct meanings were provided during the study session. New stimuli consisted of 45 foreign signs whose correct meanings were provided during the study session. The labels ‘Old’ and ‘New’ refer to the fact that the participants were likely to have known the meaning of the U.S. signs but not the foreign signs prior to testing. Relearned stimuli consisted of 45 additional randomly selected domestic road signs, which had two different meanings during the study phase: the correct meaning (Re-Old), and a new meaning (Re-New). The new meanings were randomly assigned from a bank of 45 foreign road signs not already included in the study. The assignment of domestic signs to Old or Relearned conditions was counterbalanced across participants, such that each individual received one of four possible study lists.

Training session

In a pre-scan training session, participants were provided with a crib sheet including images of all the signs they needed to learn, domestic and foreign, along with their corresponding meaning(s). They participated in three interactive computerized training blocks in which each road sign appeared on the screen, prompting them to recall aloud the meaning of the sign. For signs with two meanings, participants were asked to provide both meanings. During the training blocks, verbal feedback was given after each response, either affirming or correcting their

response. Participants alternated three times between the crib sheet and the interactive computer training, using the crib sheet to learn the meanings that they had missed during the computer blocks. The training session was self-paced, allowing the participant to spend sufficient time to learn the sign meanings, but never lasted more than 60 minutes in total.

Testing session

After the training session, participants were given instructions for the test phase, which took place while fMRI data were acquired. During testing, every sign was presented with a green or red colored border surrounding it. Green borders indicated that the participant should retrieve a sign meaning that should be pre-experimentally familiar to them; red borders cued the retrieval of a newly-learned meaning. Old and New trials were always presented with green and red borders, respectively. For signs with two meanings (Re-Old and Re-New), they were first cued to think of one of the meanings (depending on the color of the first border), and at a later point, cued to think of the other. Consequently, signs with two meanings were shown twice during scanning. The timing associated with the repetition of the second sign was completely random, occurring during either the same run or a subsequent run.

During scanning, participants viewed each sign for 3.5 s. Participants were instructed to think about the meaning of each sign as it appeared, but were not required to make an overt response to the stimulus. The rationale for not requiring overt responses during scanning was to study the retrieval of action-relevant knowledge in the absence of response requirements (Donohue et al., 2005). A short delay of 1.5 s followed each sign presentation, and periods of visual fixation lasting between 2.5s and 7.5s, jittered in increments of 2.5 s, were interleaved with the experimental trials as determined by the optimization algorithm (Dale, 1999). A total of 180 trials (45 trials per condition) were divided across three 7.5-minute fMRI scans. The order of trials within a scan was determined using an optimal sequencing program designed to maximize the separability of different conditions in a rapid event-related fMRI study (Dale, 1999).

After scanning, participants were shown each of the signs again by computer, in the same order as in the scanner. As each sign appeared on the screen, participants pressed one of three buttons to indicate how confident they were that they knew the meaning (High confidence/Low confidence/Guess). After indicating their confidence rating for a sign, participants were asked to provide the meaning of the sign to the experimenter. Although there was no explicit time limit for this task, participants frequently responded within a few seconds of being asked the meaning. Verbal responses were documented and were later scored for accuracy. Incorrect items were modeled as a separate condition and were not analyzed further. To ensure that a sufficient number of trials per condition were included in the fMRI analyses, we excluded participants who indicated the correct sign meaning for fewer than 70% of trials within a condition.

fMRI data acquisition

Scanning was performed on a 1.5T MRI scanner (General Electric Signa Advantage, Medical Advances Inc, Milwaukee Wisconsin, USA) at the University of California at Davis Imaging Research Center, using a standard whole-head coil. Visual stimuli were back-projected onto a screen that was viewed through a mirror mounted above the MRI head-coil. fMRI data were acquired using a gradient-echo echo-planar pulse sequence with the following parameters: TR =

2.5 s, TE = 40 ms, 35 axial slices, $3.44 \times 3.44 \times 3$ mm, 0.5 mm inter-slice gap, 162 volumes per run. Four functional volumes prior to each scan were discarded to allow for T1-equilibration effects. High-resolution T1-weighted coronal anatomical images were collected, and head motion was restricted using a pillow and foam inserts that surrounded the head.

fMRI data analysis

Data were preprocessed with SPM2 (Wellcome Department of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, and submitted to rigid body motion correction with sinc interpolation. Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan & Evans, 1997), an approximation of Talairach space (Talairach and Tourneaux, 1988). The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to $3 \times 3 \times 3$ mm cubic voxels. Functional volumes were spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed on individual participants' data with the general linear model implemented in SPM5. The fMRI time series data were modeled as a series of events convolved with a canonical hemodynamic response function (HRF). The resulting functions were used as covariates in a general linear model, along with a basis set of cosine functions that high-pass filtered the data, as well as a covariate for session effects. The least-squares parameter estimates of height of the best-fitting synthetic HRF for each condition were used in pair-wise contrasts, and the resulting contrast images, computed on a participant-by-participant basis, were submitted to group analyses. Incorrect trials, as determined by scoring their responses to what each sign meaning was in the post-test, were modeled as a separate condition. At the group level, contrasts between conditions were computed by performing one-tailed *t*-tests on these images, treating participants as a random effect.

In an effort to reduce the number of statistical comparisons across the whole-brain, we created anatomical masks for left and right VLPFC and for left middle temporal gyrus (MTG) using the Marsbar toolbox in SPM5 (Brett, Anton, Valabregue & Poline, 2002). The VLPFC masks each consisted of 5257 voxels (voxel size of 2^3 mm), bridging IFG orbitalis (BA 47), IFG triangularis (BA 45), and IFG opercularis (BA 44), and the left MTG mask consisted of 4942 voxels (voxel size of 2^3 mm). We then identified clusters that were activated significantly after a false discovery rate (FDR; Genovese, Lazar & Nichols, 2002) corrected threshold of $p < .05$, with a 10-voxel extent. See Table 1 for results of the whole-brain voxel-based comparisons.

Region of interest (ROI) analyses were also conducted using Marsbar (Brett et al., 2002). For each ROI, we computed the mean parameter estimates for each subject and each condition. Repeated measures ANOVA was used to examine differences across conditions, including the factors of Knowledge (old, new meaning) and Meanings (1 meaning, 2 meanings). Finally, post-hoc analyses were conducted using two-tailed dependent sample *t*-tests where appropriate.

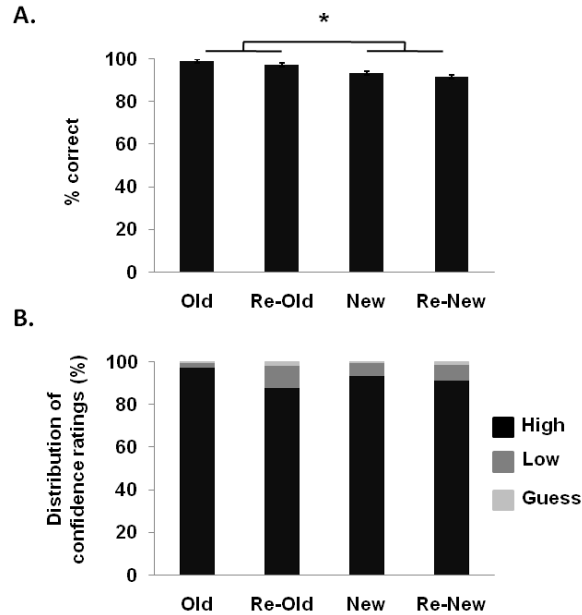


Figure 2.2. Post-scan behavioral results. (A) Data from the post-scan test indicate that although accuracy was high for all conditions (> 90%), participants correctly recalled the old items (Old, Re-Old) with greater frequency than new items (New, Re-New). The lack of a Knowledge \times Number of Meanings interaction suggests that the recovery of a particular meaning is not differentially affected by the number of meanings a sign has (at least when reaction times are not stressed). Errors bars represent the standard error of the mean. SE_m for accuracy: 0.89. $*p < .05$. (B) The distribution of confidence ratings across the four trial types indicated that participants were highly confident in their responses (confidence ratings for correct trials only). However, there was a significant tendency for Old meanings to be rated with higher confidence levels than for Re-Old, and for New meanings to show the same trend over Re-New meanings.

Results

Behavioral results from post-scan test

Accuracy was determined on the basis of the number of items in each condition that were correctly named in the post-scan session, given either the red or green border. Because participants did not respond during scanning, but rather provided a verbal explanation of the sign meanings during the post-scan session, meaningful response time data were not available for analysis. Overall, participants were highly accurate in providing the appropriate meaning(s) for the signs. A Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA revealed a significant effect of Knowledge, $F_{1, 12} = 7.56$, $p = .018$, a marginal effect of Number of Meanings, $F_{1, 12} = 3.57$, $p = .083$, and no interaction between the two, ($F < 1$; Figure 2A). These findings indicate that accuracy of retrieval was affected primarily by whether the sign meaning was old or new, and to a lesser extent by whether the sign had an additional meaning.

We then examined how confidence ratings were affected by our task manipulations (Figure 2B). Confidence ratings were significantly higher for Old than New meanings, $\chi^2(2, N = 13) = 74.34$, $p < .001$. Similarly, confidence ratings were higher for Re-Old relative to Re-New signs, $\chi^2(2, N = 13) = 19.48$, $p < .001$. Thus, participants were more confident of meanings that were known pre-experimentally. We also found that the number of meanings had an effect on confidence

ratings, such that participants were more confident of the meaning of signs with only one meaning (Old vs. Re-Old: $\chi^2(2, N = 13) = 38.41, p < .001$; New vs. Re-New: $\chi^2(2, N = 13) = 6.53, p = .038$).

Predictions for regions involved in controlled retrieval and/or selection

Before considering the results of our fMRI analyses, it is worth considering the patterns of results that could be considered as evidence of a region’s involvement in controlled retrieval and/or selection. Hypothetical data plots for these predictions can be seen in Figure 3. Figure 3A represents the predictions of a region sensitive to controlled retrieval demands. This hypothetical region is more active when participants are asked to retrieve new meanings (New, Re-New) than old meanings (Old, Re-Old), regardless of the number of meanings associated with a sign. In this plot, we make the assumption that participants retrieve *only the cued meaning* of each road sign, rather than deliberately or automatically retrieving both meanings to signs with two meanings.

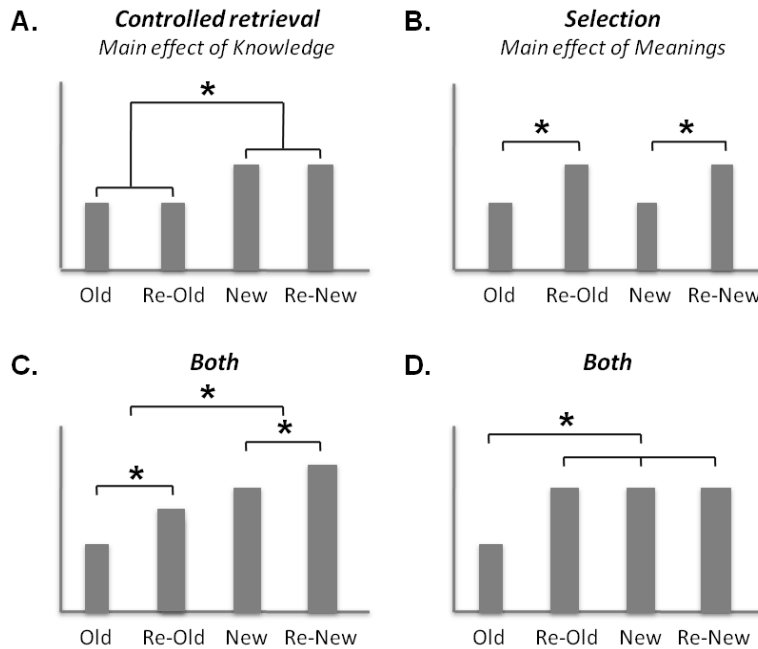


Figure 2.3. Predicted profiles of brain activation for controlled retrieval and/or selection. Y-axis values are arbitrary, and correspond to hypothetical contrast values. (A) The pattern that a pure controlled retrieval region would exhibit. This region would be exclusively driven by newly learned sign meanings, irrespective of the number of meanings associated with each sign (Re-New, New > Re-Old, Old) (B) The pattern that a pure selection region would exhibit. This region would be exclusively driven by selection demands, exhibiting greater activation for signs with two meanings irrespective of how recently the meaning was learned (Re-Old, Re-New > Old, New). Prior to examining our fMRI data, we examined how our behavioral results might inform potentially more complex predictions than the two accounts above would predict. (C) The pattern of activation for a region sensitive to both controlled retrieval and selection demands (with no interaction). Activation would be greater for newly learned meanings (New > Old, Re-New > Re-Old) as well as signs with two meanings (Re-Old > Old, Re-New > New). This pattern is drawn from the behavioral results in Figure 3A, where there was a significant effect of Knowledge and a marginal effect of Meanings (but no interaction). (D) The pattern of activation showing a Knowledge × Meanings interaction. In this hypothetical region, Re-Old, New, and Re-New activation would be significantly greater than Old. This pattern is drawn from the behavioral results in Figure 3B, where confidence ratings were highest for Old meanings, and relatively reduced for Re-Old, New, and Re-New.

Figure 3B represents what a selection account would predict for a given region. In this region, activation is greater for signs with multiple meanings (Re-Old, Re-New > Old, New), regardless of whether meanings are old or new.

In addition to the predictions above, it is possible that one or more VLPFC subregions would exhibit a more complex pattern of activation than either of the previous accounts would suggest. To explore this possibility, we looked to our behavioral results – both the accuracy and confidence rating data – for potential clues. Participants' accuracy was higher for well-known meanings, and there was a trend for higher accuracy for signs with only one meaning (Figure 2A). Mirroring this pattern of results, Figure 3C represents a region exhibiting effects of both Knowledge and Meanings. In this hypothetical plot, activation is greater for newly learned meanings (New, Re-New > Old, Re-New) as well as signs with two associated meanings (Re-Old, Re-New > Old, New). Participants' confidence ratings indicated that they were more certain of the original meaning of a sign with one meaning (Old trials) than the other sign meanings (Re-Old, New, and Re-New). Accordingly, Figure 3D represents this potential activation pattern, with activation in the Old condition reduced relative to the other conditions. In contrast to Figure 3C, this pattern of results should be marked by a Knowledge \times Meanings interaction. The ROI analyses below examine the extent to which left VLPFC subregions exhibited patterns resembling these hypothetical patterns of activation.

VLPFC analyses

We first identified all voxels in left and right VLPFC that were active relative to fixation during correct sign meaning retrieval, collapsing across the four experimental conditions (anatomically defined search space for bilateral VLPFC; $p < .05$, FDR corrected, with a minimum of ten contiguous voxels). This contrast revealed a large cluster in left VLPFC (center of mass = -46 22 13; 2609 voxels) as well as a smaller one in right VLPFC (center of mass = 54 30 27; 61 voxels) (Figure 4A). We next conducted a Region (Left, Right VLPFC) \times Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA to test for potential hemispheric differences for VLPFC. This analysis revealed no main effect of Region ($p > .70$) and no interactions with Region ($p > .30$), indicating that, although the extent of activation in left VLPFC was greater than that of right VLPFC (Figure 4A), the magnitude and profile of activation was statistically comparable between these ROIs. Accordingly, we collapsed across left and right VLPFC ROIs and conducted a Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA to test for differences in activation across our experimental manipulations. This analysis revealed a marginal main effect of Knowledge, $F_{1,12} = 4.30$, $p = .060$, an effect of Meanings, $F_{1,12} = 15.82$, $p = .002$, and an interaction between the two, $F_{1,12} = 5.27$, $p = .040$. Our significance threshold for the post-hoc tests was set to $p = .008$, correcting for six pairwise comparisons at a $p = .05$ threshold using the Bonferroni procedure. Inspection of the interaction revealed that these effects were driven by New, Re-Old, and Re-New activation being greater than Old (all $p = .002$), with no differences between New, Re-Old and Re-New (all $p > .20$). Thus, left and right VLPFC regions identified from an unbiased contrast exhibit effects of both controlled retrieval and selection, consistent with the hypothetical plot in Figure 3D.

Table 2.1

Activation table for whole-brain contrasts of interest

<i>Region of Activation</i>	<i>~BA</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>cluster size</i>	<i>z-score</i>
<i>All correct > fixation</i>						
Frontal	L6	-3	-3	57	131	4.29
Parietal	R7	27	-66	54	1764	5.45
Occipital	L19	-27	-78	42	2215	5.42
Cingulate	L31	-6	-36	30	122	4.21
	L23	-3	-54	15	15	3.52
Caudate	L	-18	0	15	563	4.85
<i>New > Old</i>						
Frontal	L44/9	-48	15	27	148	4.72
	L45	-39	24	18	19	4.15
	L47	-42	15	-3	67	4.08
	R47	39	24	-3	35	3.85
Parietal	L39	-30	-57	36	39	3.79
	L40/7	-39	-42	48	14	3.60
Occipital	L19	-30	-75	24	19	3.74
	R19	30	-75	39	40	3.72
Cingulate	R24	9	-3	36	12	4.53
Caudate	L	-6	6	12	44	3.97
	R	12	12	9	24	3.85
<i>Re-Old > Old</i>						
Frontal	L9	-54	12	39	269	4.45
	L47	-42	18	-3	112	4.11
	L6	-9	3	54	19	3.97
	L46/10	-36	39	21	18	3.37
	R9	54	9	39	73	4.22
	R46/10	27	45	9	26	3.92
	R10	30	66	12	26	3.74
Parietal	L40/7	-42	-48	48	481	4.81
	R7	21	-72	51	33	3.99
	R40/7	51	-45	51	74	3.91
Occipital	L18/19	-30	-66	-12	21	4.15
	L19	-3	-78	42	34	3.49
Insula	R	36	18	0	47	3.85
Cingulate	R32	12	12	39	17	3.90

Note: Each whole-brain group contrast is set at a threshold of $p < .001$, uncorrected for multiple comparisons, with a minimum of five contiguous voxels. ~BA = approximate Brodmann's area.

Dissociable activation profiles within left VLPFC

The large cluster in left VLPFC (Figure 4A) was identified from a general contrast of all conditions relative to fixation. We sought to determine whether a subset of the voxels within this large cluster would be engaged specifically by controlled retrieval and/or selection demands. To this end, we computed three masked contrasts aimed at testing for regions exhibiting one of the four predicted activation profiles (Figure 3).

To identify regions specifically involved in controlled retrieval (Figure 3A), we conducted the following contrast: New > Old ($p < .05$, FDR corrected, with a minimum of ten contiguous voxels), excluding voxels engaged even weakly by the selection manipulation, Re-Old > Old ($p < 0.1$, uncorrected for multiple comparisons, with no extent threshold). To identify regions specifically involved in selection (Figure 3B), we conducted the opposite contrast: Re-Old > Old ($p < .05$, FDR corrected, with a minimum of ten contiguous voxels), excluding voxels engaged even weakly by the controlled retrieval manipulation, New > Old ($p < 0.1$, uncorrected for multiple comparisons, with no extent threshold). For both of these masked contrasts, we only further considered clusters of at least ten contiguous voxels. Finally, to identify regions in left VLPFC sensitive to both the controlled retrieval and selection (Figure 3C-D), we computed activation maps for sensitive to controlled retrieval (New > Old, $p < .05$, FDR corrected, with a minimum of ten contiguous voxels) and selection (Re-Old > Old, $p < .05$, FDR corrected, with a minimum of ten contiguous voxels). No activation was present at the ten voxel threshold, so we then relaxed the voxel threshold to five for this contrast.

These masked contrasts yielded three small clusters within left VLPFC (Figure 4B-D). The contrast sensitive to controlled retrieval revealed a cluster in aVLPFC (BA 47; center of mass at MNI coordinates of [-52 29 -2]). The contrast sensitive to selection demands revealed activation in a more posterior extent of VLPFC (pVLPFC; BA 44/9; [-37 11 25]). Finally, the contrast sensitive to both controlled retrieval and selection revealed a cluster in mid-VLPFC (BA 44/9; [-50 15 29]). ROI analyses were conducted to fully characterize the activation profiles of these regions across all four conditions (Figure 4B-D). These analyses, described below, show differential sensitivity to controlled retrieval and selection demands, respectively.

Signs with two meanings were shown twice during scanning, and we were concerned that sign repetition might have influenced retrieval and/or selection on the second presentation, and therefore activation values in our ROIs. Thus, for each ROI described below, we performed a Knowledge (old, new) \times Repetition (first, second presentation) repeated measures ANOVA for signs with two meanings (i.e., for the Re-Old and Re-New conditions). In the event that we found an effect of Repetition or a Knowledge \times Repetition interaction, we conducted a follow-up analysis focusing solely on the first presentation of a sign with two meanings. If there was no effect of Repetition, we collapsed across repetitions and no longer considered it a factor in the analysis.

The aVLPFC cluster (BA 47; [-52 29 -2]; Figure 4B - right) was identified based on the fact that it was more active for New than Old trials, but not for Re-Old than Old trials. A Knowledge \times Repetition repeated measures ANOVA focusing on signs with two meanings revealed no effect of Repetition, $F_{1,12} = 1.04$, $p = .33$, but there was a hint that repetition was differentially

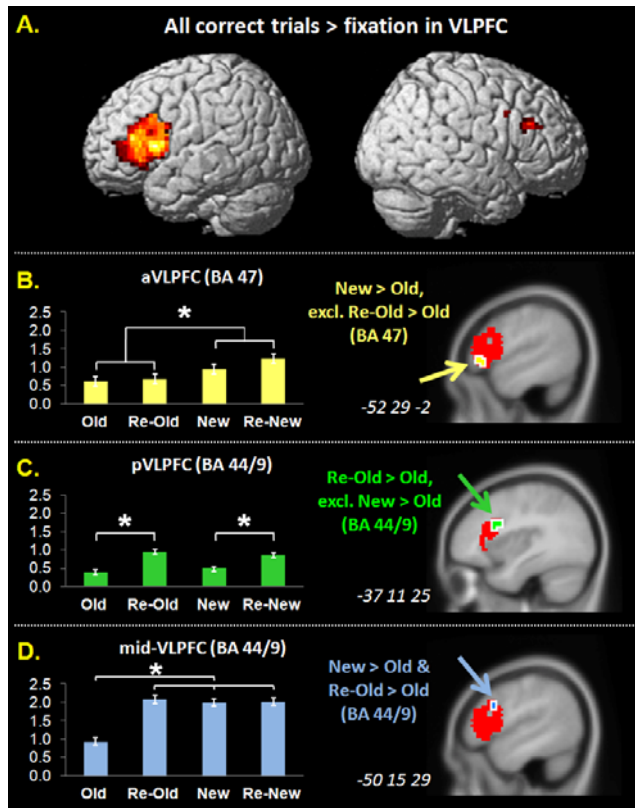


Figure 2.4. Left VLPFC activation and ROI analyses. (A) Group contrast of all correct sign meaning retrievals relative to fixation, anatomically constrained to left and right VLPFC only ($p < .05$, corrected for multiple comparisons using false discovery rate (FDR), with a minimum ten voxel extent threshold, Genovese et al., 2002). Robust activation in left VLPFC can be observed (left), while a smaller extent of activation can be observed in right VLPFC (right). (B) Functional ROI in anterior VLPFC (aVLPFC; BA 47; [-52 29 -2]), which was derived by taking the group contrast of activation for New > Old ($p < .05$, FDR corrected, minimum ten voxel threshold extent), and masking out voxels even weakly engaged by selection demands (Re-Old > Old, $p < .10$, no threshold extent) (right). Activation in this region was driven by controlled retrieval demands, with greater activation for New and Re-New relative to Old and Re-Old (left), as predicted in Figure 3A. Note that activation values for Re-Old and Re-New are for the first presentation of a sign only, as a Knowledge \times Repetition interaction revealed reduced activity for Re-New on the second presentation of the sign (See Figure 5A for the second presentation). (C) Functional ROI in posterior VLPFC (pVLPFC; BA 44/9; [-37 11 25]), which was derived by taking the group contrast of activation for Re-Old > Old ($p < .05$, FDR corrected, minimum ten voxel threshold extent), and masking out voxels even weakly engaged by controlled retrieval demands (New > Old, $p < .10$, no threshold extent) (right). Activation in this region was driven by selection demands, with greater activation for Re-Old than Old and Re-New than New (left), as predicted in Figure 3B. Note that Re-Old and Re-New activation values are for the first presentation of a sign only, as an effect of Repetition revealed reduced activation for both trial types on the second presentation (See Figure 5B for the second presentation). (D) Functional ROI in mid-VLPFC (BA 44/9; [-50 15 29]), which was derived by examining clusters larger than five continuous voxels (no activation present at ten voxels) that survived a conjunction analysis between New > Old ($p < .05$, FDR corrected, minimum five voxel threshold extent) and Re-Old > Old ($p < .05$, FDR corrected, minimum ten voxel threshold extent). Activation in mid-VLPFC was driven by controlled retrieval and selection demands, with greater activation Re-Old, New and Re-New, as predicted in Figure 3D. Brodmann areas cited for each region are approximations based on the Talairach atlas (Talairach and Tournoux, 1988). The Y-axis values correspond to contrast values, and the error bars represent the standard error of the mean. The reported coordinates are based on MNI space, and coordinates associated with each ROI correspond to their center of mass.

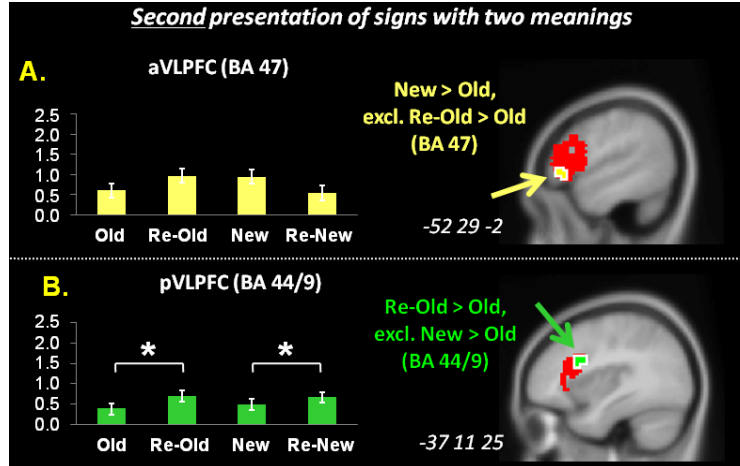


Figure 2.5. Functional ROIs in left VLPFC for the second presentation of a sign. Acquisition of these functional ROIs was identical to the methods described in Figure 4B-C. (A) In aVL PFC (right), a repeated measures ANOVA revealed a marginal Knowledge \times Meanings interaction, $F_{1,12} = 4.50, p = .055$ (main effects of Knowledge and Meanings *ns*, $F_{1,12} < 1$) (left). This activation pattern is a marked departure from the pattern of results obtained from including only the first presentation of a sign (see Figure 4B). (B) In pVL PFC (right), a repeated measures ANOVA revealed similar results to the analysis constrained to only the first sign presentation (main effect of Meanings, $F_{1,12} = 10.73, p = .007$, effect of Knowledge and interaction *ns*, $F_{1,12} < 1$), though the magnitude of the Meanings effect is attenuated by the second presentation. Brodmann areas cited for each region are approximations based on the Talairach atlas (Talairach and Tournoux, 1988). The Y-axis values correspond to contrast values, and the error bars represent the standard error of the mean. The reported coordinates are based on MNI space, and coordinates associated with each ROI correspond to their center of mass.

influencing activation values for Re-Old and Re-New (Knowledge \times Repetition interaction, $F_{1,12} = 4.44, p = .064$). Post-hoc tests revealed that this effect was fueled by a significant reduction in activation for Re-New trials during the second presentation of the sign, $t_{12} = 2.79, p = .016$ (Re-Old difference *ns*, $p > .30$). Accordingly, we limited our subsequent analyses in aVL PFC to the first presentation of a sign (see Figure 5 for the activation profile associated with the second presentation). A Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA revealed that aVL PFC activation on the first presentation of a sign was primarily driven by the effect of Knowledge, $F_{1,12} = 10.68, p = .007$ (main effect of Meanings and interaction *ns*, $F_{1,12} < 1$) (Figure 4B - left). This pattern observed in left aVL PFC is consistent with a role in controlled retrieval, as in the hypothetical plot in Figure 3A.

The pVL PFC cluster (BA 44/9; [-37 11 25]; Figure 4C - right) was identified based on the fact that it was more active for Re-Old than Old trials, but not for New than Old trials. A Knowledge \times Repetition repeated measures ANOVA examining the effects of sign repetition revealed that Re-Old and Re-New values were significantly reduced during the second presentation of a sign, $F_{1,12} = 6.93, p = .022$ (Knowledge \times Repetition interaction *ns*, $F_{1,12} < 1$). Accordingly, we limited our subsequent analyses in pVL PFC to the first presentation of a sign (see Figure 5 for the activation profile associated with the second presentation). A Knowledge \times Meanings repeated measures ANOVA only revealed a strong effect of Meanings, $F_{1,12} = 27.06, p < .001$ (effect of Knowledge *ns*, $F_{1,12} < 1$; interaction *ns*, $F_{1,12} = 2.22, p = .16$) (Figure 4C - left). This

pattern in left pVLPFC is consistent with a role in selection, as in the hypothetical plot in Figure 3B.

We then sought to test whether the activation profiles of left aVLPFC and pVLPFC were functionally distinct. A Region (aVLPFC, pVLPFC) \times Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA revealed differential modulation between the regions for Knowledge (Region \times Knowledge interaction, $F_{1,12} = 6.88, p = .022$). Additionally, there was a non-significant trend for differential modulation with respect to Meanings (Region \times Meanings interaction *ns*, $F_{1,12} = 3.49, p = .087$; Region \times Knowledge \times Meanings interaction *ns*, $F_{1,12} = 1.81, p = .204$). In sum, left aVLPFC modulation was driven significantly more by controlled retrieval demands than was left pVLPFC. In contrast, left pVLPFC exhibited a trend towards being driven more strongly by selection demands than left aVLPFC.

Finally, we sought to identify a cluster within left VLPFC that was sensitive both to controlled retrieval and selection demands, consistent with the hypothetical plots in Figure 3C-D. We identified a cluster of activation in mid-VLPFC (BA 44/9; [-50 15 29]; Figure 4D – right) by performing a conjunction analysis between manipulations sensitive to controlled retrieval and selection demands. The repetition analysis revealed no significant effect of Repetition and no Knowledge \times Repetition interaction (both $F_{1,12} < 1$). As such, we collapsed across sign repetitions for the subsequent analysis. A Knowledge \times Meanings repeated measures ANOVA revealed a significant effect of Knowledge, $F_{1,12} = 28.75, p < .001$, an effect of Meanings, $F_{1,12} = 12.89, p = .004$, and a significant interaction, $F_{1,12} = 29.12, p < .001$ (Figure 4D – left). Activation in this ROI was, by definition, greater for New than Old and Re-Old than Old signs. Additionally, we found that it was more active for Re-New than Old signs, $t_{12} = 5.21, p < .001$. This pattern, functionally distinct from both aVLPFC and pVLPFC, but similar to that of the larger left VLPFC cluster from which these small clusters had been isolated, is consistent with a role in both controlled retrieval and selection.

Left posterior middle/inferior temporal gyrus

The general contrast of all conditions relative to fixation that yielded ROIs in left and right VLPFC also yielded a cluster in left posterior middle/inferior temporal gyrus (BA 21/20; [-54 -46 -8]). The coordinates of this region fell within the cluster that we had identified in our prior study involving road signs (Donohue et al., 2005). A Knowledge \times Repetition repeated measures ANOVA revealed that sign repetition did not differentially influence activation profiles between Re-Old and Re-New meanings in this region (main effect of Repetition *ns*, $F_{1,12} < 1$; Knowledge \times Repetition *ns*, $F_{1,12} = 1.13, p = .309$). Consistent with the findings of Donohue et al., 2005, a Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA revealed that this region was not sensitive to controlled retrieval demands, $F_{1,12} < 1$. We also found that this region, while engaged during task performance in this study, was insensitive to selection demands $F_{1,12} = 1.17, p = .301$ (interaction *ns*, $F_{1,12} < 1$).

Cognitive conflict associated with signs with two meanings

Because we did not assess behavior during scanning, and could not have gotten a meaningful response time measure from the post-scan test, we sought assurances that our manipulation of number of sign meanings was effective in eliciting competition between possible meanings. To

this end, we conducted one additional ROI analysis, focusing on the anterior cingulate cortex (ACC) – a region that is reliably engaged when participants must monitor their performance, either because a task is challenging, or because they have just made an error, or because they must select between competing responses (Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004).

In the present study, a region within the “cognitive” division of the ACC (Bush, Luu & Posner, 2000) was evident in the whole-brain contrast of Re-New > New (BA 32; [-7 19 36]; $p < .005$, uncorrected for multiple comparisons, with a minimum 10 voxel extent threshold). This finding was predicted, given that the Re-New condition requires participants to focus on a newly learned sign meaning while ignoring the more familiar meaning of a sign with two meanings. After finding no significant effect of repetition (effect of Repetition *ns*, $F_{1,12} = 1.35$, $p = .268$; interaction *ns*, $F_{1,12} = 1.02$, $p = .333$), we conducted an ROI analysis to characterize the activation profile of this region. The ACC was not significantly modulated by Knowledge, $F_{1,12} < 1$, but there was an effect of Meanings, $F_{1,12} = 9.79$, $p = .009$ (interaction *ns*, $F_{1,12} = 1.15$, $p = .305$). We consider this finding a ‘proof of concept’ that the Re- conditions were associated with higher selection demands than the Old and New conditions. Like other recent studies (e.g., Mitchell, Heatherton, Kelley, Wyland, Wegner et al., 2007), our results indicate that this region in the ACC is not exclusively involved in detecting response conflict, as there were no overt responses during the task.

Discussion

The main goal of the present study was to examine the contributions of VLPFC subregions to the retrieval and selection of action-relevant knowledge. To this end, we adapted the design of our prior study (Donohue et al., 2005), including road signs with well-known or newly-learned meanings, as well as signs with one or two meanings. This design allowed us to compare the effects of a controlled retrieval manipulation of new versus old sign meanings, and a selection manipulation of signs with two versus one meaning(s). As expected, behavioral accuracy was lower for newly-learned relative to well-known meanings. Accuracy for signs with two meanings was comparable to accuracy for signs with one meaning. However, participants’ confidence ratings indicate that they were significantly less confident about their response when the sign meaning was recently learned, or when a sign had more than one meaning.

Left and, to a lesser extent, right VLPFC were engaged while participants viewed the road signs and retrieved the associated meaning(s), consistent with our prior work (Figure 2.4A) (Donohue et al., 2005). With the modified design used in the present study, we found that the vast majority of the large left VLPFC cluster was more active whenever a sign had a new meaning associated with it (New, Re-Old, and Re-New trials) than when it did not (Old trials), regardless of which meaning participants had been asked to retrieve. A similar pattern was obtained for the smaller cluster in right VLPFC. This pattern is consistent with the hypothetical plot in Figure 2.3D, suggesting sensitivity to both controlled retrieval and selection demands.

Based on prior studies involving judgments regarding semantic associations between words (i.e. Badre et al., 2005), we had predicted that our manipulations would differentially engage

subregions of left VLPFC (Figure 2.3). Our region in left aVLPFC (BA 47; [-52 29 -2]) was driven by our manipulation of whether or not the sign meaning had been recently learned, and in fact it is located near a cluster that Badre and colleagues reported (-51 27 -3) as being most affected a manipulation of associative strength (Figure 2.4B). Our region in left pVLPFC (BA 44/9; [-37 11 25]) was driven relatively more by our manipulation of the number of meanings associated with a sign (Figure 2.4C), and is consistent with other studies implicating this region in selection (Kan & Thompson-Schill, 2004; Thompson-Schill et al., 1997; Thompson-Schill et al., 1999). Finally, our mid-VLPFC cluster (-50 15 29) showed sensitivity to both controlled retrieval and selection manipulations (Figure 2.4D). Thus, as proposed by Badre and colleagues (2005), mid-VLPFC may serve as a convergence zone, anatomically and functionally intermediate to regions involved in controlled retrieval (aVLPFC) and post-retrieval selection (pVLPFC).

The ability to access and utilize goal-relevant information from long-term memory is a critical aspect of everyday behavior. In the present study, we examined how we access potentially important information from cues in the environment, and select from among the information that is most relevant for guiding action. Although we found regions in aVLPFC and pVLPFC modulated specifically by controlled retrieval or selection demands, respectively, the large cluster in left VLPFC (as well as the one in mid-VLPFC) revealed sensitivity to both demands. The findings support the notion that left VLPFC supports the retrieval of action-based semantic knowledge from long-term memory in support of goal-directed behavior.

Chapter 3

Over the course of a given day, we interact rather automatically with many familiar objects, drawing on a long history of interactions with similar objects. How do we represent the functions of these objects and the actions that we must undertake to use them properly? Deficits in these two types of object-related knowledge – knowledge-*of*-action and knowledge-*for*-action (Badre, 2008) – are evident in patients with specific types of apraxia. Patients with *ideomotor apraxia*, who typically have left parietal damage or damage to the connections between left parietal and frontal cortex, often understand what an object is used for (and perhaps how to use it), but have difficulty performing the goal-directed movements associated with it (Heilman, Rothi & Valenstein, 1982; Haaland, Harrington & Knight, 2000; for review, Zadikoff & Lang, 2005). By contrast, patients with *ideational apraxia*, who often have damage to left parietal and fronto-temporal regions, have a more severe knowledge deficit: they demonstrate an impoverished understanding of how tools can be used in a goal-directed manner on relevant objects (Ochipa, Rothi & Heilman, 1989; for review, Zadikoff & Lang, 2005). Research with these patient groups suggests that function knowledge, impaired in ideational apraxia, and action knowledge, impaired in ideomotor apraxia, may rely on partially distinct brain networks that, under normal conditions, act in concert to guide knowledge-guided behavior with objects (Bozeat et al., 2002).

Consistent with these neuropsychological data, functional neuroimaging studies have identified a largely left-lateralized network of frontal, parietal, and temporal lobe regions engaged when participants perform mental tasks involving manipulable objects (for review, Martin & Chao, 2001; Johnson-Frey, 2004; Lewis, 2006). In particular, these regions include the posterior third, roughly, of the middle temporal gyrus (pMTG; Brodmann's Area [BA] 21), ventrolateral prefrontal cortex (VLPFC, BA 44/45), premotor cortex (BA 6), and inferior (IPL; BA 40) and superior (SPL; BA 7) parietal cortex. These neuroimaging data are broadly consistent with neuropsychological evidence that damage to left posterior temporal lobe is associated with impairments in object knowledge (Damasio et al., 1996; Bozeat et al., 2002). The primary goal of this study was to better characterize the contribution of left pMTG to object knowledge.

Left pMTG has been implicated in a number of neuroimaging studies involving manipulable objects across various task demands, including viewing or naming tools or generating or making judgments on tool-relevant action words (Martin et al., 1995; Damasio et al., 1996; Martin, Wiggs, Ungerleider & Haxby, 1996; Chao, Haxby & Martin, 1999; Perani et al., 1999; Okada et al., 2002; Grossman et al., 2002; Kounios et al., 2003; Corina et al., 2005; Saccuman et al., 2006; Yalachkov, Kaiser & Naumer, 2009), viewing tool motion (Beauchamp, Lee, Haxby & Martin, 2002, 2003), action and/or function knowledge decisions with object images or words (Devlin et al., 2002; Kellenbach et al., 2003; Boronat et al., 2005; Noppeney et al., 2005; Canessa et al., 2008), identifying objects based on the sounds they make (Lewis et al., 2004; Lewis et al., 2005), imagining using a tool (Creem-Regehr & Lee, 2005) and planning to use a tool (Johnson-Frey, Newman-Norlund & Grafton, 2005).

Our group has previously found that left pMTG is also engaged when participants retrieve behavioral rules from long-term memory, such as the fact that a triangular red and white road sign indicates that we should yield to oncoming traffic (Bunge et al., 2003; Donohue et al.,

2005). Using abstract symbols like road signs, we found that a visual stimulus arbitrarily associated with a rule for behavior was sufficient to engage left pMTG, suggesting that this region is not specific to tool knowledge *per se*, but is more generally involved in representing semantic information about the actions and/or functions represented by, or associated with, a stimulus (Bunge, 2004).

Martin & Chao (2001) have argued that left pMTG represents action knowledge, or features of motion, associated with objects. This view stems from a number of observations, including (1) activation in left pMTG across a number of studies for verb naming and the viewing of manipulable tools is largely overlapping (Martin, 2001), (2) left pMTG is adjacent to visual area MT, a cortical region involved in general motion processing (Maunsell & Van Essen, 1983), and (3) left pMTG is adjacent to left posterior superior temporal sulcus, a cortical region involved in the processing of biological motion (Beauchamp, Lee, Haxby & Martin, 2003; Beauchamp, Lee, Argall & Martin, 2004). Further support for this view is drawn from studies in which pMTG is activated when implied motion is suggested in static images (Kourtzi & Kanwisher, 2000; Senior et al., 2000) and in which pictures of animals associated with specific actions are presented (Tyler et al., 2003). However, it is still unclear whether left pMTG represents action knowledge, as Martin & Chao (2001) suggest, and/or function knowledge associated with objects. We sought to clarify this matter in the present study.

A secondary focus of this study was to examine the role that VLPFC plays in processing object knowledge. Left VLPFC activation has been observed in many of the same studies of action knowledge as left pMTG (for review, Johnson-Frey, 2004; Lewis, 2006). In the cognitive control literature, left anterior VLPFC (aVLPFC; BA 45/47) has been implicated in the controlled retrieval of semantic information from long-term memory (Wagner et al., 2001; Badre et al., 2005; Souza, Donohue & Bunge, 2009). Thus, it has been argued that VLPFC retrieves and maintains online the information that is needed to guide action selection (Wagner et al., 2001; Curtis and D'Esposito, 2004; Bunge et al., 2005; for review, Bunge, 2004). The secondary goal of this study was to examine VLPFC engagement during the retrieval of functional semantics (i.e. what the object is used for) and action semantics (i.e. how one moves one's body to use the object properly).

We asked participants to view images of manipulable objects and to perform one of four mental tasks while viewing each image (Table 3.1). The "Function" condition required participants to retrieve conceptual information stored in long-term memory about the primary use of an object, whereas the "Imagery" condition required participants to retrieve motor information about how to properly handle and use the object for its primary purpose. The "Repeat" condition required participants to rehearse the most prominent color in the object image while the "Rotate" condition asked participants to imagine rotating the object along a surface. Repeat served as the control condition for Function because it was also verbal but did not require retrieval of knowledge about the functions or actions associated with specific objects. Similarly, Rotate was the control condition for Imagery because it was also a form of motor imagery (functionally distinct from visual imagery, Sirigu & Duhamel, 2001) but did not require imagery of actions associated with specific objects.

We reasoned that if left pMTG represents conceptual function knowledge about visual stimuli, activation in this region should be strongest when participants retrieve function knowledge about an object (Function), relative to when they imagine using the object (Imagery), imagine rotating the object along a surface (Rotate), or mentally rehearse the name of a prominent color in the object (Repeat). In contrast, if left pMTG is involved in representing the movements associated with object use, this region should be most active for the Imagery condition.

We also sought to characterize the contribution of VLPFC to action knowledge representation. Considering that left VLPFC has a role in the controlled retrieval of semantic knowledge (Wagner et al., 2001), we expected it to be most active for the Function task, which requires the retrieval of semantic knowledge about the object's use. However, it was an open question as to whether VLPFC would be active during the Imagery task, which requires the participant to imagine using the object. Finally, we expected that VLPFC would be weakly engaged by the control tasks, Repeat and Rotate, which do not require retrieval of object-specific knowledge.

Several important features of this study should be noted. First, stimulus assignment to the conditions was counterbalanced across participants, such that any differences in brain activation that we observe between conditions should be related to the mental task being performed, rather than intrinsic properties of the stimuli (e.g. object affordances). Second, participants made no overt responses during scanning – an aspect of task design that we considered critical for a study focusing on action representations. Finally, we acquired post-scan measures of memory and self-reported judgments of ability to carry out the task.

Methods

Participants

Thirteen healthy native-English speaking adults (4 male, $M = 22.6$ yrs, range = 20-27) were compensated for their participation in the study. One additional participant, separate from the set just described, was excluded after revealing that she had dyslexia. All participants had normal or corrected-to-normal vision and audition and were right-handed as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971). The study was approved by the Office of Research and the Institutional Review Board at the University of California, Davis.

Stimuli

Before embarking on the fMRI study, we took 153 color photos of manipulable objects, and recruited eight UC Davis undergraduates (a different pool from the participants in the fMRI study) to name each object and describe its primary function. We used these ratings to exclude object images that were difficult to name and/or to ascribe a function. We then retained the top 100 images for use in the study (Table 3.2).

fMRI task

Prior to scanning, the experimenter explained that the participant would be asked to think about common objects in different ways, based on one of four task instructions. On a given trial, a fixation cross would alert them to the beginning of the trial, and then one of four instructions would appear on the screen: Function, Imagery, Repeat or Rotate (Figure 1A). The instructions required participants to either (1) consider how they would describe the purpose of the object to

Table 3.1. Experimental conditions

<u>Task</u>	<u>Task Description</u>	<u>Action or function knowledge?</u>	<u>Task Domain</u>
Function	Describe the primary use of the object	Yes	Verbal
Repeat	Rehearse a prominent color name in the object	No	
Imagery	Imagine using the object in a typical fashion	Yes	Visuospatial
Rotate	Imagine rotating the object along a surface	No	

someone (“Function”), (2) imagine themselves using the object in the way that it is typically used (“Imagery”), (3) identify and verbally rehearse the most prominent color of the object (“Repeat”), or (4) imagine themselves rotating the object 180 degrees along the surface (“Rotate”) (Table 3.1). Shortly after the onset of the instruction, an object image was presented below the instruction and the participant was to perform the mental task with the object. Inter-trial intervals of 2-6s were inserted between trials based on an optimization algorithm designed to separate trial-by-trial functional activations in a fast, event-related design (Dale, 1999).

After learning the meanings of the four instructions, participants practiced the task with 28 sample trials (7 per condition). Object images used during the practice session were distinct from those used in the fMRI task. Participants performed the task silently during the practice phase, just as they were instructed to do during scanning. Upon completion, the experimenter confirmed that the participant thoroughly understood the instructions and was comfortable with the pace of the task. After successful completion of the practice session, participants were informed that they would complete two sessions of the task, with each being followed by a brief memory test.

fMRI data acquisition

The entire set of 100 images was presented on each of two runs, with 25 images per condition in each run. For the second run, object images were associated with their task counterpart (photos previously assigned to the Imagery condition in the first run were now associated with Rotate, and Function with Repeat) so that each condition ultimately consisted of 50 trials. Run order was counterbalanced across participants, and the assignment of objects to a particular condition was also counterbalanced.

fMRI data were collected with an 8-channel phased-array coil on the 3T Siemens TRIO MRI scanner at the University of California, Davis, Imaging Research Center (<http://ucdir.ucdavis.edu/>). The experiment was projected onto a screen that was viewed through a mirror mounted above the MRI head-coil. Two runs of functional data were acquired using a gradient-echo echo-planar pulse sequence with the following parameters (TR = 2.0 s, TE = 25 ms, 34 axial slices, 3.4 × 3.4 × 4 mm, no interslice gap, 263 volumes per run). Four volumes at the onset of each functional run were discarded to allow for T1-equilibration effects, yielding a total of 518 volumes per participant for fMRI data analysis. High-resolution T1 MPRAGE coronal anatomical images were also collected. Head motion was restricted through the use of foam inserts that surrounded the head.

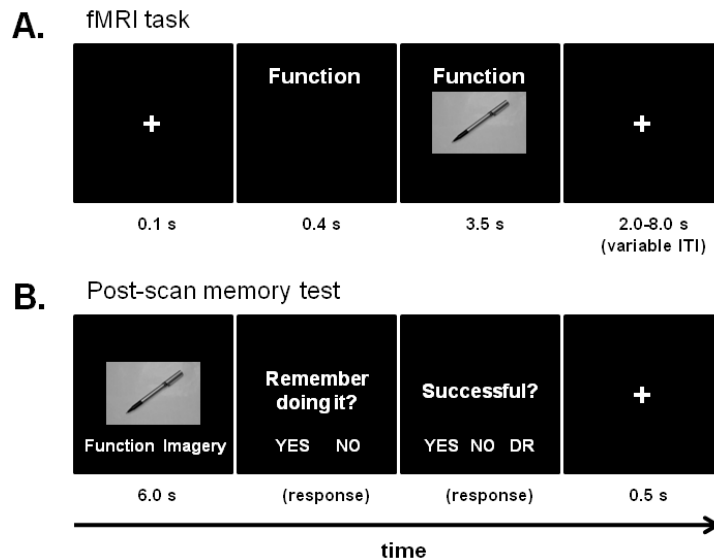


Figure 3.1. Event-related fMRI and post-scan memory test procedures. A) During scanning, each trial consisted of one randomly assigned instruction with a photo of an object. During this time, the participant would think about the object in the way prescribed by the instruction (Table 3.1). Variable ITI's, as indicated by a white fixation cross, were randomly interspersed between trials. B) The post-scan memory test probed subjective memory for the tasks performed during scanning. Participants decided (1) whether a given object had been associated with the Function or Imagery instruction, (2) whether they could recollect having performed the trial or not (“Remember doing it?”), and (3) whether they were able to perform the trial without interference from other tasks (“Successful?”). All object images were presented in full color, and a list of the objects used can be found in Table 3.2.

Post-scan memory task

Although we did not collect behavioral responses during scanning, we did conduct a memory test after each of the two scans in an effort to gauge participants’ compliance with the task instructions. The logic of these post-scan tests was that if participants actively imagined using a stapler, they would be more likely to later remember that they had imagined using the stapler rather than explaining its function, when presented with the stapler again. To avoid participant fatigue and possible confusion, we limited the post-scan memory tests to items that had been associated, in one scan, with one of the two contrasts of greatest interest: Function and Imagery. (In the other scan, such items were associated with the corresponding verbal or visual imagery control condition – never with the other condition of interest.)

During the two post-scan tests, which were conducted immediately after each of the two runs, an object image seen in the previous run would appear, and participants would have to choose which of two conditions it had been associated with during the previous scan: Function or Imagery (Figure 1B). Next, participants were prompted to indicate whether or not they could recollect having performed the appropriate task with the object. Finally, they were asked how well they had been able to perform that trial *without* performing any of the other mental tasks or thinking unrelated thoughts. These ratings were used to identify trials to be excluded from fMRI analysis: namely, the trials for which participants explicitly noted that they had had difficulty carrying out the task instructions, as well as trials for which they incorrectly indicated which task they had performed for a given image on the preceding scan.

Table 3.2. List of objects included in the study

Baseball	Garlic Press	Masking tape roll	Spatula
Baseball bat	Guitar	Mixer	Spinning top
Basketball	Hair comb	Mug	Sponge
BBQ tongs	Hammer	Nail clippers	Spray bottle
Broom	Hand brush	Needle-nose pliers	Staple remover
Calculator	Hand dumbbell	Paper fastener	Stapler
Can opener	Hand exerciser	Paperclip	Stopwatch
Cheese grater	Hand mallet	Pasta scooper	Tape dispenser
Chopsticks	Hand pump	Peeler	Tape measure
Clothes pin	Hand saw	Pencil	Tennis racquet
Cola can	Handheld yard clippers	Pill bottle	Toothbrush
Cologne spray bottle	Hose nozzle	Pizza slicer	Toy gun
Computer mouse	Ice cream scooper	Pliers	Typewriter
Cordless drill	Iron	Plunger	Umbrella
Crochet needle	Ketchup bottle	Push broom	Videogame controller
Dental floss	Kitchen sponge	Pushpin	Water container
Dustpan	Kleenex	Putty knife	Water glass
Electric razor	Ladle	Razor	White out
Eyeliners	Large knife	Remote control	Wine opener
Fire extinguisher	Large paintbrush	Rolling pin	Wisk
Flashlight	Light switch	Salad tongs	Wisk broom
Fly swatter	Lighter	Scissors	Wrench
Football	Lint roller	Screwdriver	Wrench
Fork	Lipstick	Scrub brush	Yard shears
Frisbee	Loofah	Soap pump	Yo-yo

fMRI data analysis

Data were preprocessed with SPM2 (Wellcome Department of Cognitive Neurology, London). Differences in slice acquisition timing were corrected, and the volumes were subjected to a rigid-body motion correction with sinc interpolation. Structural and functional images were spatially normalized to T1 and EPI templates, respectively. The normalization procedure consisted of a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization, the volumes were re-sampled to $3 \times 3 \times 4$ mm voxels. Images were then smoothed using an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed on individual subjects' data with the general linear model implemented in SPM2. The fMRI time series data were modeled as a series of events convolved with a canonical hemodynamic response function (HRF). Presentation of the instruction and the image were modeled as a single impulse function. The least-squares parameter estimates of height of the best-fitting synthetic HRF for each condition were used in pair-wise contrasts. The

Table 3.3. List of studies used to construct left pMTG spherical ROIs

<u>Study</u>	<u>Whole-brain contrast</u>	<u>x</u>	<u>y</u>	<u>z</u>	
<u>ROI 1</u>					
Donohue et al. (2005)	<i>Correct > incorrect road sign meanings</i>	-56	-40	2	
<u>ROI 2</u>					
Boronat et al. (2005)	<i>Function - function baseline (words)</i>	-56	-60	-10	
Johnson-Frey et al. (2005)	<i>Executing > preparing tool gestures</i>	-52	-64	4	
Kellenbach et al. (2003)	<i>Action > non-manipulable function</i>	-48	-62	0	
	<i>Manipulable > non-manipulable function</i>	-52	-52	0	
	<i>Action > control</i>	-46	-60	-4	
	<i>Manipulable function > control</i>	-52	-50	-2	
Kounios et al. (2003)	<i>Implements > animals</i>	-57	-42	23	
	<i>Implements > abstract nouns</i>	-53	-30	18	
Devlin et al. (2002)	<i>Man-made > natural items</i>	-64	-34	-12	
Grossman et al. (2002)	<i>Implement > animal words</i>	-61	-54	15	
Okada et al. (2000)	<i>Tools > animals</i>	-50	-52	-8	
Chao et al. (1999)	<i>Viewing tools > animals</i>	-46	-57	6	
	<i>Naming tools > animals</i>	-45	-59	10	
	<i>Reading tools > animals</i>	-49	-53	0	
Perani et al. (1999)	<i>Non-living > meaningless shapes</i>	-57	-47	-6	
	<i>Non-living > living</i>	-44	-58	3	
		Median coordinates:	-52	-54	0
<u>ROI 3</u>					
Beauchamp et al. (2002)	<i>Tool > human videos</i>	-46	-70	-4	
Beauchamp et al. (2003)	<i>Tool > human videos</i>	-50	-62	-6	
		Median coordinates	-48	-66	-5

Note: All reported coordinates are in MNI space.

resulting contrast images, computed on a subject-by-subject basis, were submitted to group analyses. Trials excluded on the basis of the post-scan tests were modeled as a separate condition and excluded from further analysis. At the group level, whole-brain contrasts between conditions were computed using one-tailed t tests on the contrast images, treating subjects as a random effect. Task-related activation was considered significant in the whole-brain exploratory group contrasts at $p < .001$, uncorrected for multiple comparisons, with a 10-voxel extent threshold.

Region of interest (ROI) analyses were conducted using the Marsbar toolbox in SPM2 (Brett et al., 2002; <http://marsbar.sourceforge.net/>) to further characterize the activation profiles of left pMTG. Our primary analysis approach for left pMTG involved the construction of four 8-mm radius spherical ROIs centered on maxima from prior studies (Table 3.3). A secondary interest in this experiment was to examine the activation profiles in VLPFC. Functional ROIs in left and right VLPFC were drawn from a whole-brain contrast designed to identify regions involved in accessing object-specific action/function knowledge (Function, Imagery > Repeat, Rotate). For each of these ROIs, mean contrast values were computed for each subject and condition for each ROI, and were then submitted to a Type (verbal vs. visuospatial) \times Knowledge of Use (required vs. not) repeated measures (RM) ANOVA. Where necessary, post-hoc tests were conducted using dependent sample t tests.

Results

Behavioral results from post-scan test

We examined participant accuracy for correctly associating objects with the instructional rule, the proportion of trials they indicated they remember having performed, and the success with which they were able to carry out the task as requested (Table 3.4). There were no reliable differences in accuracy or remember ratings between Function and Imagery, but there was a reliable difference among the Success ratings. Success ratings of “Yes,” which indicate that the participant was able to think about the object in the way instructed by the rule without being off-task or considering other rules, did not significantly differ between the conditions. However, participants had significantly fewer ‘No’ and ‘Don’t Remember’ responses for the Imagery condition. In sum, participants exhibited equally good accuracy and memory for Function and Imagery, but reported greater success in carrying out the task instructions for the Imagery trials.

Whole-brain comparisons

Viewing of manipulable objects

We first sought to characterize the network of brain regions engaged during the viewing of manipulable objects. A group contrast comparing all four task conditions to baseline revealed activation in left VLPFC (BA 44/45/46), left middle frontal gyrus (BA 9), dorsal premotor cortex (BA 6), bilateral IPL (BA 40), left SPL (BA 7), bilateral putamen, bilateral cerebellum, and bilateral motor cortex (BA 4). This pattern of activation, which was more strongly lateralized to the left hemisphere, is consistent with previous literature demonstrating a role for these regions in supporting object knowledge (Johnson-Frey, 2004; Lewis, 2006).

Table 3.4. Post-scan Memory Test Results

	<i>Condition</i>	<i>Remember</i>	<i>Success</i>		
	<i>Accuracy (%)</i>	<i>Yes (%)</i>	<i>Yes (%)</i>	<i>No (%)</i>	<i>DR (%)</i>
Function	86.6	88.5	75.7	6.6	16.5
Imagery	87.1	88.8	83.2	3.8	10.6
	<i>ns</i>	<i>ns</i>	<i>ns</i>	*	**

Note: Repeated measure ANOVA and/or paired sample *t* tests were used to test for differences in accuracy and Remember ratings, and Chi-Square tests were used to test for differences in Success ratings. DR = Don't Remember. ** $p < .005$; * $p < .05$; *ns* = not significant at $p < .05$.

Retrieval of object-specific action or function knowledge

Next, to explore the network of regions involved in accessing action and/or function-relevant object knowledge, we compared the Imagery and Function conditions to their respective control conditions (Figure 3.2A). The contrast Function > Repeat, which aimed to isolate regions involved in the retrieval of function knowledge, revealed activation in left pMTG (BA 21) and left VLPFC (BA 45, 47). The contrast Imagery > Rotate, which aimed to isolate regions supporting object-specific action knowledge (while controlling for motor imagery), revealed a different pattern of activation, including a partially distinct portion of left VLPFC (BA 44, 47) and left premotor cortex (BA 6). For a complete list of activations and coordinates for both of these contrasts, as well as a contrast sensitive to the main effect of object action knowledge (Function + Imagery) > (Repeat + Rotate), please refer to Table 3.5.

ROI analyses

Left pMTG and nearby regions in temporal cortex

Our primary focus was to characterize the activation profile of four spherical ROIs in the left posterior temporal lobe, centered on coordinates from prior studies: (1) the local maximum in left pMTG from a previous study in our laboratory examining the retrieval of *rules* specifying actions associated with road signs (-56 -40 2; Donohue et al., 2005), (2) the median coordinates from a number of studies examining action and function knowledge associated with objects (-54 -52 0; list of studies available in Table 3.3), (3) the median coordinates of a region in posterior inferior temporal cortex shown to respond to *tool motion* (~BA 37; -49 -68 -2; Beauchamp et al., 2002; 2003) and (4) the local maximum of a region in pMTG shown to respond to *biological motion* (BA 22/39; -39 -62 18; Beauchamp et al., 2002). As can be seen in Figure 3.2B (upper-right panel), ROIs 1-3 were spatially distinct and progressed from anterior to posterior in left pMTG.

pMTG ROI 1

In the left pMTG sphere centered on the coordinates of our prior study on retrieval of the meanings of road signs (Donohue et al., 2005), we observed a main effect of Type, $F(1,12) = 38.78$, $p < .0001$, a main effect of Knowledge of Use, $F(1,12) = 16.44$, $p < .002$, and a trend towards a Type \times Knowledge of Use interaction, $F(1,12) = 3.80$, $p = .075$ (Figure 3.2B: ROI 1). Indeed, the main effects and marginal interaction were driven by activation in the Function

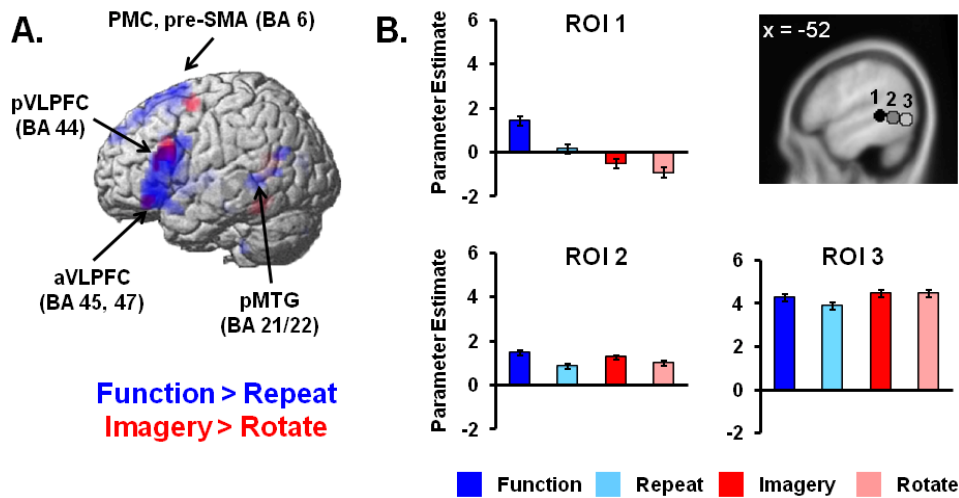


Figure 3.2. Whole-brain group contrasts and ROI analyses in left pMTG. A) Significant activations are shown in blue for Function > Repeat, and in red for Imagery > Rotate. There was extensive activation of left anterior and posterior VLPFC in the Function > Repeat contrast, as well as activation in left pMTG. Statistical threshold for this group contrast was set to $p < .001$ uncorrected for multiple comparisons, with a 10-voxel extent. B) Location of three 8-mm spherical ROIs centered on coordinates reported from a set of prior studies on action knowledge (Table 3.3). *ROI 1*: A region identified by a prior study examining behavioral rule retrieval (Donohue et al., 2005; -56 -40 2). In the present study, this region was specifically activated during the Function condition ($t[12] = 3.38, p = .005$). *ROI 2*: A more posterior region in the left temporal lobe identified by acquiring the median coordinates from a set of prior action studies (Table 3.3; -54 -52 0). In the present study, this region was more engaged by accessing action/function knowledge (Function, Imagery > Repeat, Rotate; $F[1,12] = 8.06, p < .015$). *ROI 3*: The most posterior ROI in left pMTG was identified based on two prior studies examining cortical processing of tool motion (Beauchamp et al., 2002; 2003; -49 -68 -2). In this ROI, there were no significant differences between the conditions ($ps > .1$). All coordinates are reported in MNI space; error bars represent standard errors of the mean.

condition, which was the only condition significantly engaged above baseline, $t(12) = 3.38, p = .005$ (Repeat *ns*, $t(12) < 1, p > .60$).

pMTG ROI 2

We next sought to determine how activity in left pMTG related to other studies of object-specific action knowledge, as we had observed that these studies generally identified somewhat more posterior foci in left pMTG than the region identified in Donohue et al. (2005). We acquired the median coordinates from a number of studies examining object-specific action and function knowledge (-54 -52 0; Table 3.3) and indeed confirmed that this location was posterior to the Donohue sphere (Figure 2: upper-right panel). In contrast to what we found in ROI 1, this relatively more posterior ROI was sensitive only to whether object knowledge was required, $F(1,12) = 8.06, p < .015$ (Type *ns*, $p > .80$; Interaction *ns*, $p > .1$), exhibiting greater activation for Function and Imagery than Repeat and Rotate conditions (Figure 3.2B: ROI 2). Thus, unlike the more anterior region in pMTG described above, this region was engaged whenever object-specific action or function knowledge was required, either through semantic retrieval or through motor imagery.

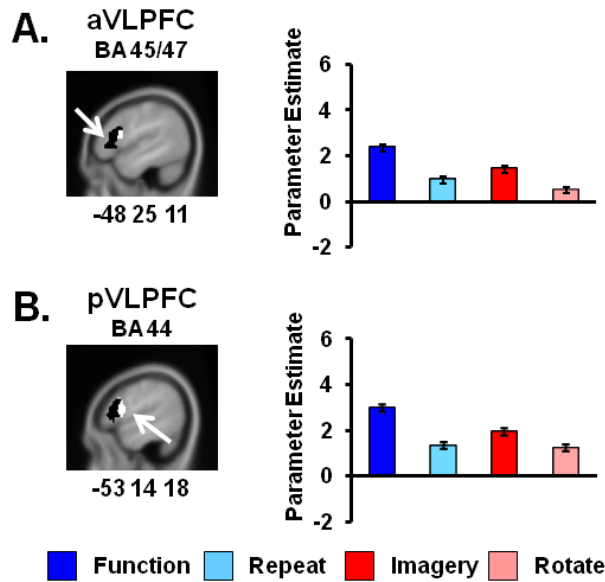


Figure 3.3. Functional ROI localization and analyses in left VLPFC. Activation was identified from the whole-brain contrast in Experiment 1 sensitive to object action/function knowledge (Function, Imagery > Repeat, Rotate). This contrast produced a large swath of activation in left VLPFC which we then broke up into the anatomical subdivisions of the inferior frontal gyrus: *pars triangularis* (aVL PFC) and *pars opercularis* (pVL PFC). (A) In addition to exhibiting a main effect of Knowledge, by definition based on the contrast that produced this ROI, aVL PFC also exhibited a main effect of Type ($p < .001$), with stronger activation for the verbal conditions than the visuospatial ones. (B) pVL PFC also exhibited a main effect of Type ($p = .009$), as well as a Knowledge \times Type interaction ($p = .006$). This interaction was fueled by greater activation for Function than Imagery ($p = .005$; Repeat vs. Rotate ns , $p > .40$). Error bars represent standard errors of the mean.

pMTG ROIs 3 and 4

Finally, we sought to determine whether activation in these pMTG regions differed from regions in left posterior temporal cortex found in previous studies to be strongly responsive to tool motion and biological motion (Table 3.3). Unlike the other ROIs, the tool motion ROI (Figure 3.2B: ROI 3) was strongly and indiscriminately engaged across all four conditions; indeed, a Type \times Knowledge of Use RM ANOVA revealed no significant differences across our conditions (main effects and interaction ns , $ps > .1$). The biological motion ROI was not significantly engaged relative to baseline for any of the conditions (all $p > .10$; not shown).

VLPFC

As noted previously, a secondary focus of this study was to characterize the activation profiles in VLPFC across our four task conditions. We were able to identify activation in left anterior and posterior VLPFC and right anterior VLPFC from the whole-brain contrast between conditions that did vs. did not require retrieval of object knowledge (Function, Imagery > Repeat, Rotate). Because the swath of activation in left VLPFC was extensive, we used Marsbar to mask this cluster with two anatomical sub-regions of left VLPFC: the more anterior *pars triangularis* (aVL PFC; BA 45/47) and the more posterior *pars opercularis* (pVL PFC; BA 44/45). For each of the ROIs in VLPFC, we used a Type \times Knowledge of Use RM ANOVA to examine whether these regions were additionally modulated by Type, or a Type \times Knowledge of Use interaction.

Table 3.5. Activation table for whole-brain contrasts of interest

<i>Region of Activation</i>	<i>~BA</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i># voxels</i>	<i>z-score</i>
<i>(Function + Imagery) > (Repeat + Rotate)</i>						
Inferior frontal	L47	-42	30	-8	392	4.74
	L45	-42	27	12	-	4.35
	L44	-54	18	20	-	4.30
Inferior frontal	L45/47	54	36	4	25	3.90
Medial frontal	L11	-3	39	-16	14	3.73
Middle frontal	L6	-42	3	60	27	4.19
Superior frontal	L8/9	-9	57	36	88	4.03
Middle temporal	L21/22	-48	-42	0	53	4.37
Thalamus	-	-12	-9	0	25	4.21
Putamen	-	-18	6	0	16	3.65
Cingulate	L32	-12	24	32	178	4.62
	L30	-6	-54	12	161	4.96
Visual	L17	-9	-90	4	17	3.60
	L19	21	-93	32	77	4.18
	R19	48	-81	12	42	4.66
Cerebellum	-	18	-69	-32	22	3.52
<i>Function > Repeat</i>						
Inferior frontal	L45	-57	21	20	524	5.04
	L47	-45	27	-12	-	4.61
Superior frontal	L6	-6	12	68	210	4.58
Dorsal frontal	L32	-6	21	36	20	3.67
Middle temporal	L21	-51	-45	0	38	3.61
	L39	-48	-63	20	15	3.77
	R37	57	-69	4	11	3.66
Cuneus	L18	6	-78	16	18	3.35
Cerebellum	-	30	-57	-24	152	4.07
	-	0	-36	-48	12	3.73
<i>Imagery > Rotate</i>						
Inferior frontal	L44/46	-48	18	24	55	4.40
	L47	-33	33	-12	17	3.68
	R45/46	51	36	4	13	3.37
Middle frontal	L6	-42	3	60	18	4.16
Fusiform	L37	-39	-48	-16	23	3.84
Cingulate	L23/31	-6	-57	16	75	4.54

In aVLPFC (BA 45/47), we observed a main effect of Type, $F(1,12) = 23.66, p < .001$, but the interaction was not significant, $F(1,12) = 2.65, p = .129$ (Figure 3.3A). Activation in aVLPFC was more engaged for the verbally-based conditions (Function, Repeat) as well as conditions requiring knowledge of use (Function and Imagery, by definition). In pVLPFC (BA 44/45), we observed a main effect of Type, $F(1,12) = 9.86, p = .009$, and an interaction between the two, $F(1,12) = 11.23, p = .006$ (Figure 3.3B). Activation in pVLPFC was greater for Function than Imagery, $t(12) = 3.48, p = .005$, and Repeat and Rotate did not significantly differ, $t(12) < 1$. Thus, left aVLPFC and pVLPFC were sensitive to action and function knowledge retrieval demands, but pVLPFC was more engaged for Function than Imagery, and least for both Repeat and Rotate.

In contrast to left aVLPFC and pVLPFC, right aVLPFC was only sensitive to the effect of Knowledge of Use (Main effect of Type and interaction *ns*, $F(1,12) < 1$ and $F(1,12) = 1.61, p = .23$, respectively). Thus, unlike left VLPFC, right VLPFC was not preferentially engaged by verbal task demands. In summary, left VLPFC was more strongly engaged by verbal demands, and both left and right VLPFC were more engaged for the conditions that required retrieval of object-specific knowledge.

Discussion

In this study, we examined the role of left pMTG and VLPFC in the retrieval of knowledge about the functions and actions associated with manipulable objects. Specifically, we tested whether left pMTG represents semantic knowledge about a manipulable object's function and/or the actions associated with it. We posited that if left pMTG represents function knowledge, this region should be most active when accessing conceptual knowledge about an object's function. In contrast, if this region represents action knowledge, it should be more active when retrieving knowledge about how to move your arm and hand when using the object.

Participants viewed images of objects and thought about (1) the purpose of the object (Function), (2) using the object (Imagery), (3) a prominent color of the object (Repeat), or (4) turning the object upside-down along a surface (Rotate). In the anterior-most ROI in left pMTG (ROI 1), which was identified by Donohue et al. (2005) for the retrieval of rules associated with road signs (-56 -40 2), we found that this region was exclusively activated by the retrieval of conceptual knowledge about the function of the object (Figure 3.2B – ROI 1). Taken together, activation in this region is consistent with a role in representing function knowledge associated with visual stimuli – both images of real objects, as shown in the present study, as well as of abstract symbols (Donohue et al., 2005).

A slightly more posterior region in pMTG (ROI 2), identified from a number of previous studies examining action and/or function knowledge, revealed greater activation for both Function and Imagery (Figure 3.2B), consistent with a more general role in action knowledge associated with visual stimuli (Bunge, 2004), including manipulable objects but also animals (Tyler et al., 2003). Even more posterior, a region identified by coordinates from two previous studies involving the processing of tool motion (Beauchamp et al., 2002; 2003) revealed strong but indiscriminant activation across our four conditions (Figure 3.2B). The most posterior of our four ROIs, based

on a study examining biological motion (Beauchamp et al., 2002), was not engaged relative to baseline in this study. These results suggest that conceptual knowledge about actions associated with visual stimuli may be represented in a relatively more anterior portion of left pMTG, spatially distinct from regions processing the physical movements associated with the use of these objects. Furthermore, these findings support a knowledge gradient in left pMTG such that conceptual knowledge is supported in a more anterior extent (~ROI 1) and action knowledge is supported more posterior (~ROI 2).

With respect to VLPFC, previous work has implicated left aVLPFC (BA 45/47) in controlled, effortful retrieval of semantic information (Vandenberghe et al., 1996; Gabrieli et al., 1998; Wagner et al., 2001; Badre et al., 2005; Souza, Donohue & Bunge, 2009), and this implication extends to the tool knowledge literature (for review, Lewis, 2006). Consistent with this role, left aVLPFC was engaged by Function relative to Repeat trials. The fact that this region was also engaged more strongly by Imagery relative to Rotate trials further underscores the general role of this region in retrieval of both action and function knowledge associated with objects.

Left posterior VLPFC (BA 44/6) has been associated with post-retrieval selection of goal-relevant information (Thompson-Schill et al., 1997; Badre et al., 2005; Kan et al., 2006), verbal working memory (Gabrieli et al., 1998), as well as the representation of how tools can be used in a goal-directed manner (Johnson-Frey, Newman-Norlund & Grafton, 2005). In the present study, pVLPFC was most engaged by Function, followed by Imagery, and finally Repeat and Rotate. This pattern of activity is consistent with a role in verbal semantic processing.

Limitations of the present study

It is important to note that it is possible that the pattern of results we observed in left pMTG, specifically the finding in ROI 1, may be a product of verbal generation demands, as opposed to fundamental differences between the task conditions and the types of knowledge they require. The verbal demands of the Function task were almost certainly greater than the Repeat condition, let alone the Imagery and Rotate conditions. Unfortunately, the design of the present study does not allow us to rule out this possibility. In an attempt to rule out this possibility, we now move to a follow-up fMRI study (Chapter 4), using an expanded set of tool images and a set of three verbal conditions with more comparable difficulty.

Chapter 4

Retrieving knowledge from long-term memory about how to interact with manipulable objects is an important, frequently utilized cognitive ability. As described in the previous chapters, there is growing evidence that under normal circumstances, both left VLPFC and left pMTG provide important contributions to this process (for review, Johnson-Frey, 2004; Lewis, 2006). While the precise role of left VLPFC in semantic processing is still being debated (for opposing views, see Thompson-Schill et al., 1997; Wagner et al., 2001), the nature of the contribution of left pMTG in representing action-relevant knowledge is also unclear.

As detailed in Chapter 3, activation in left pMTG is frequently observed in studies involving manipulable objects (for review, Martin & Chao, 2001; Johnson-Frey, 2004; Lewis, 2006). Martin and Chao (2001) have suggested that this region may support features of movement, or action knowledge, associated with manipulable objects. However, findings from our laboratory involving the retrieval of rules (e.g., Bunge et al., 2003; Donohue et al., 2005) suggest that left pMTG may play a more general role in representing semantic knowledge about the actions and/or functions associated with a visual stimulus (Bunge, 2004).

In an attempt to further examine this hypothesis, we designed an fMRI study (Chapter 3; Souza, Donohue & Bunge, 2009) where participants considered different types of information about manipulable objects, as directed by a task cue. We manipulated whether or not participants considered information relevant to the object's use, as well as whether they thought about the object in a verbal or visuospatial manner (see Table 3.1 for a list of conditions). In a spherical ROI we created in left pMTG, which was anchored by the local maxima in this region during the successful retrieval of road sign meanings (Donohue et al., 2005), we observed strong and exclusive activation for the retrieval of verbal semantics related the object's canonical use. These findings are consistent with our hypothesis that left pMTG supports the representation of function semantic knowledge about stimuli in our environment.

Unfortunately, features in our task design have limited our ability to make stronger claims about the precise contribution of left pMTG. Most notably, it is possible that the activation we observed in this ROI in left pMTG was driven by task difficulty, rather than true differences between the types of knowledge being accessed. Because we did not collect subjective ratings of rule difficulty from each fMRI subject, we were unable to rule out this possibility. To retest our hypothesis about the nature of knowledge representations supported by left pMTG, we designed this follow-up study to address these concerns.

The present study

As in the previous study, we asked participants to view images of manipulable objects and to think about them in a way consistent with a given task cue. We adapted the task cues in the present study so that each required the participant to think about the object in a verbal manner (Table 4.1). We retained the "Function" condition, which required participants to consider semantic knowledge about the object's typical use, and also added two new conditions. In the "Action" condition, participants were asked to describe the body movements one used when using an object in a typical manner. Finally, in the Appearance condition, we asked participants

Table 4.1. Experimental conditions

<u>Task</u>	<u>Task Description</u>	<u>Action or function knowledge?</u>	<u>Task Domain</u>
Function	Describe the primary use of the object	Yes	
Action	Describe how you move your hands/arms when using the object	Yes	All Verbal
Appearance	Describe the physical characteristics of the object (e.g. color, shape, texture)	No	

to describe the physical features of the object, including its color, shape and/or component materials. Now equipped with more comparable conditions, we conducted a behavioral pilot prior to the fMRI study to confirm that the Function condition was not the most difficult.

After properly addressing the issue of task difficulty, we once again hypothesized that the region we examined in left pMTG in the previous study (Figure 3.2B – ROI 1), which was exclusively engaged by the Function condition, would be most active for the Function condition. We also reasoned that the next most posterior ROI (Figure 3.2B – ROI 2), which was equally engaged for Imagery and Function in the prior study, would be equally engaged for both Action and Function. Finally, we expected no differences between the conditions in the next posterior ROI (Figure 3.2B – ROI 3), consistent with the findings of the previous study.

Methods

Participants

Fifteen native-English speaking adults (2 male, $M = 21.2$ yrs, range = 18-26), none of whom had participated in the previous experiment or the behavioral pilots, were compensated for their participation in the study. Three additional participants were excluded from the fMRI analyses because of poor performance on the “Successful” rating aspect of the Post-scan Memory test (>30% unsuccessful ratings for at least one of the conditions). All participants had normal or corrected-to-normal vision and audition and were right-handed as determined by the Edinburgh Handedness Questionnaire (Oldfield, 1971). All study methods and procedures were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley.

Stimuli and pilot ratings

We added 20 images to the pool of 100 images used in the previous experiment so that images would not be repeated during the experiment, as was previously the case (Table 4.2). These additional images were comparable in terms of basic visual features and complexity. We conducted a behavioral pilot with 12 UC Berkeley undergraduates, separate from the pool of fMRI participants in Experiments 1 and 2. The goals of this pilot were to (1) determine whether the new 20 images were as easy to identify as the previous set of 100, and (2) examine potential differences in difficulty across our modified set of conditions. Each participant rated on a scale from 1 (very easy) to 5 (very difficult) how difficult it was to think of a given object paired with one of the new instructions.

Table 4.2. List of objects used in the study

Bar of soap*	Frying pan*	Mason jar*	Scrub brush
Baseball	Funnel*	Math compass*	Soap pump
Baseball bat	Garlic Press	Mixer	Spatula
Basketball	Guitar	Mug	Spinning top
BBQ tongs	Hair comb	Nail clippers	Sponge
Binoculars*	Hammer	Nail polish remover*	Spray bottle
Broom	Hand brush	Needle-nose pliers	Staple remover
Calculator	Hand dumbbell	Nut cracker*	Stapler
Can opener	Hand exerciser	Old-style telephone*	Stopwatch
Cheese grater	Hand mallet	Paint brush*	Tape dispenser
Chopsticks	Hand pump	Paper fastener	Tape measure
Clothes pin	Hand saw	Paperclip	Tennis racquet
Cola can	Handheld yard clippers	Pasta scooper	Tobacco pipe*
Cologne spray bottle	Hose nozzle	Peeler	Toothbrush
Computer mouse	Ice cream scooper	Pencil	Toy gun
Cordless drill	Iron	Pepper grinder*	Tweezers*
Crochet needle	Ketchup bottle	Pill bottle	Typewriter
Dart*	Key*	Pizza slicer	Umbrella
Dental floss	Kitchen sponge	Pliers	Videogame controller
Dustpan	Kleenex	Plunger	Water container
Egg slicer*	Ladle	Push broom	Water glass
Electric razor	Large knife	Pushpin	White out
Eyeglasses*	Large paintbrush	Putty knife	Wine glass*
Eyeliners	Light switch	Razor	Wine opener
Fire extinguisher	Lighter	Remote control	Wisk
Flashlight	Lint roller	Rolling pin	Wisk broom
Fly swatter	Lipstick	Rubik's cube*	Wrench
Football	Loofah	Salad tongs	Wrench
Fork	Magnifying glass*	Scissors	Yard shears
Frisbee	Masking tape roll	Screwdriver	Yo-yo

Note: * indicates that this object image was added for the present study.

The results revealed that the new 20 images were in line with the other 100 images and that, although the participants found all of the conditions to be relatively easy to consider, there were reliable differences in terms of difficulty. Specifically, Appearance was rated as the most difficult condition (mean rating: 2.37), followed by Action (mean rating: 1.87) and then Function (mean rating: 1.55) (all differences significant at $p < .005$). Indeed, all 12 subjects rated Function as the easiest of the three conditions. Post-rating questions revealed that Appearance was often rated as the most challenging because the number of relevant elements to report numbered far more than the other conditions. Also, several participants found it somewhat odd at first to verbalize the body movements associated with object use (Action), though all reported having acclimated to this demand after a number of practice trials.

fMRI task

As in the previous study, the experimenter instructed the participant to think about the objects in different ways, now based on one of three instructions (Table 4.1). The three conditions required participants to sub-vocally characterize certain aspects of the objects, including how they would describe (1) the purpose of the object to someone (Function), (2) the way in which they move their arm(s) and hand(s) to use the object (Action), or (3) the physical features of the object, such as its color, shape, and component parts (Appearance).

The fMRI task timings were adapted from the previous study to provide participants slightly more time to generate the appropriate response based on the task instruction (see Figure 3.1A). In the present study, pre-trial fixation lasted 0.5s, the instructional rule was present for 1.5s, and the rule and object image were presented for 3.0s, resulting in a total trial time of 5.0s. Inter-trial intervals of 2.5-7.5s were inserted in the same manner previously described (Dale, 1999).

Participants first memorized the instructional rules and then practiced the task on a computer outside of the scanner. They received 24 practice trials, 8 trials per instructional rule, using object images not included in the fMRI task. As in the previous study, participants practiced using the instructions and acclimating to the trial timing. Next, the participants were informed that they would complete two sessions of the task, each followed by a brief memory test to examine their memory for the mental tasks they had performed.

fMRI data acquisition

The collection of 120 object images was split equally across the two runs so that each run contained 20 trials for each condition, yielding a total of 40 trials for each condition. Run order and instructional rule and object pairings were counterbalanced between subjects.

fMRI data were collected with an 32-channel phased-array coil on the 3T Siemens TRIO MRI scanner at the Brain Imaging Center at the University of California, Berkeley (<http://bic.berkeley.edu>). The stimuli were projected onto a screen that was viewed through a mirror mounted above the MRI head-coil. Two runs of functional data were acquired using a gradient-echo echo-planar pulse sequence with the following parameters (TR = 2.5 s, TE = 25 ms, 38 axial slices, $3.0 \times 3.0 \times 2.5$ mm, 0.5 mm inter-slice gap, 182 volumes per run). This resulted in 364 volumes per participant across the two runs. Prior to data acquisition for each run, four dummy volumes were acquired and subsequently discarded to allow for T1-equilibration effects. High-resolution T1 MPRAGE coronal anatomical images were also collected. Head motion was limited through the use of foam inserts surrounding the head.

Post-scan memory task

We conducted a post-scan memory test after each of the two runs to ensure that participants were on-task during the functional scans. The test format was identical to the test in the previous study except for one adjustment: Participants now had to choose which of the *three* conditions the object was associated with. In the previous study's fMRI analysis, we had filtered out trials where participants chose the incorrect rule or had provided a Success rating of "No" for a given object/condition combination. However, the present memory test was more difficult, as all conditions were verbal and there were now three possible answers. Therefore, we reasoned that

Table 4.3. Post-scan Memory Test Results

	<u>Condition</u>	<u>Remember</u>	<u>Success</u>		
	Accuracy (%)	Yes (%)	Yes (%)	No (%)	DR (%)
Action	76.4	91.2	79.4	4.1	16.5
Appearance	86.3	90.3	80.5	3.9	15.2
Function	75.7	92.1	71.1	8.2	20.8
	*	<i>ns</i>	<i>ns</i>	*	~

Note: Repeated measure ANOVA and/or paired sample *t* tests were used to test for differences in accuracy and Remember ratings, and Chi-Square tests were used to test for differences in Success ratings. DR = Don't Remember. * $p < .005$; $\sim p = .07$; *ns* = not significant at $p < .05$.

participants might well have performed the task as instructed during scanning but be unable to remember the rule/image associations correctly later. As such, we excluded only the trials for which participants had provided a rating of “No” on the Success component.

fMRI data analysis

Data were preprocessed and analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London) using same procedures described previously. ROI time course analyses for left pMTG ROIs 1-3 as well as the functionally-defined activations for left aVLPFC and pVLPFC (as described in the previous study) were conducted using the Marsbar toolbox available for SPM5 (Brett et al., 2002; <http://marsbar.sourceforge.net/>). BOLD time series data was extracted for each run and was averaged across all voxels in each ROI for each of the three task conditions. We adjusted the onset of each condition for each participant to zero and then averaged the data to produce group plots for each task condition. To compare the time course profiles between conditions in the left pMTG ROIs, we computed the mean of the time course values at 5.0 and 7.5s, capturing the peaks for the three conditions across the ROIs. The same procedure was done for the left VLPFC ROIs, but the averaged time window was shifted in time to both 7.5 and 10.0 s, taking into account the slightly later peaks relative to the left pMTG ROIs. We submitted these values to a one-way RM ANOVA with three levels (Action, Appearance, Function). Where necessary, post-hoc tests were conducted using dependent sample *t* tests.

Results

Behavioral results from post-scan test

Due to technical complications, post-test data for one participant was not available, resulting in full behavioral data for 14 participants (Table 4.3). For the condition matching choice, accuracy was higher for Appearance than both Action and Function. For the remember choice, ratings of “Yes” were equally frequent and did not differ across conditions. For the success ratings, participants reported a good deal of success in being able to carry out the task instructions. Success ratings of “Yes” were relatively frequent and did not differ between the conditions. However, the Function condition received more “No” ratings and there was a tendency towards receiving more “Don’t Remember” ratings.

Because our primary interest was in a participant's ability to carry out the mental operations associated with each condition (and not their memory for these actions), we only excluded trials for which participants distinctly recalled having difficulty with a given trial, as indicated by a success rating of "No" – i.e., approximately 4-8% of trials, depending on the condition. Across participants, the number of trials included in the fMRI analyses did not significantly differ between the conditions, $\chi^2(2, N = 14) < 1$.

Whole-brain contrasts

Task-specific activation

We first conducted three separate group contrasts designed to reveal brain regions most strongly engaged by each task condition (Figure 4.1). After removing the common activation with Action and Appearance, the Function condition only revealed one cluster of activation, located in left pMTG (center of mass: -60 -39 3), very close to the ROI from the road sign study we examined in the prior experiment (-56 -40 2; ROI 1). The Action condition, after removing the effects of Appearance and Function, revealed a wide spread left-lateralized network including left VLPFC, premotor cortex, parietal cortex and pMTG. Importantly, the loci of activation in left pMTG for Function and Action were spatially distinct (see Figure 4.1, inset), but the space between these clusters was significantly activated by both conditions relative to Appearance (see Figure 4.2, inset). Finally, activation greater for the Appearance condition, after filtering out common activation with Action and Function, revealed only right hemisphere regions, including posterior

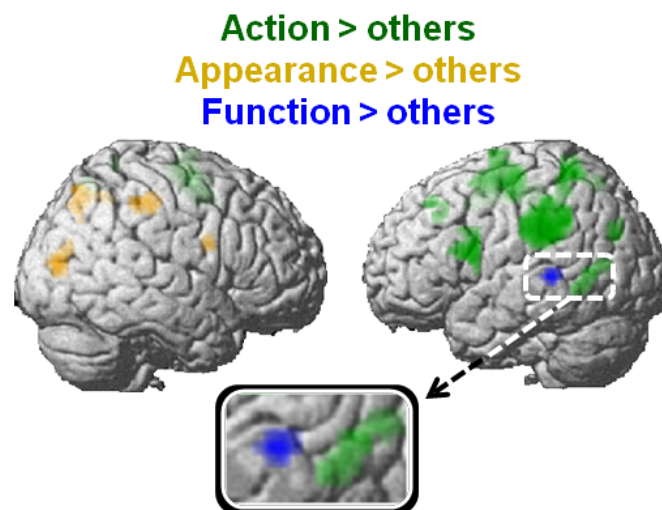


Figure 4.1. Whole-brain group contrasts for each condition. Significant activation for Action > Appearance and Function (shown in green), Appearance > Action and Function (yellow), and Function > Action and Appearance (blue). The Function contrast reveals only one cluster of activation, located in left pMTG. The Action contrast reveals an extensive network of regions, including pVLPFC (BA 44) and DLPFC (BA 9), premotor cortex and pre-SMA (BA 6), IPL (BA 40) and SPL (BA 7), and left pMTG (BA 21). The Appearance contrast reveals right-lateralized frontal, parietal, and occipital regions. The inset shows a closer view of the left posterior temporal cortex, with a distinct cluster of activation in the more anterior pMTG for Function and a cluster for Action in the more posterior extent. These contrasts were set to a statistical threshold of $p < .001$ uncorrected for multiple comparisons, with a 10-voxel extent threshold.

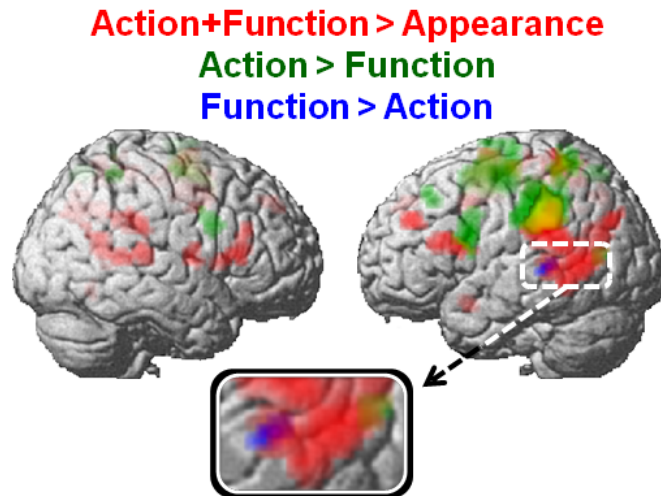


Figure 4.2. Additional whole-brain group contrasts of interest. Significant activation for the common activations for Action and Function > Appearance (shown in red), Action > Function (green) and Function > Action (blue). There is extensive overlap between Action and Function in frontal, parietal and temporal cortices. A region in the anterior IPL (yellow) was engaged in a graded fashion across the conditions (Action > Function > Appearance). The inset below shows a zoomed-in view of the left posterior temporal cortex (same anatomical location as in Figure 3), which shows the distinct clusters for Function and Activation, respectively, but common activation in the area intermediate to these clusters. All three contrasts were set to a statistical threshold of $p < .005$ uncorrected for multiple comparisons, with a 10-voxel extent threshold.

frontal, parietal and occipital cortices. In sum, the Function condition engaged the same region of left pMTG as the previous experiment (ROI 1), while Action and Appearance engaged a widespread network of frontal and parietal cortices in the left and right hemisphere, respectively.

ROI analyses

Left pMTG and nearby regions in temporal cortex

We next sought to test the hypothesis that the more anterior extent of left pMTG is most engaged by accessing function knowledge. Thus, we examined the same spherical ROIs in the previous experiment to test for differences between our task conditions.

pMTG ROI 1

In the first study, an ROI analysis revealed that this region, which was drawn from a previous study requiring the retrieval of behavioral rules (Donohue et al., 2005), was exclusively driven by the Function condition. In the present study, an analysis of the time courses revealed a significant difference between the conditions, $F(2,28) = 5.79$, $p = .008$, and as predicted, this was fueled by greater activation for Function relative to both Action and Appearance, $t(14) = 2.23$, $p = .042$ and $t(14) = 3.69$, $p = .002$, respectively (Figure 4.3 – ROI 1). Thus, even after considering task difficulty, this region in left pMTG was most engaged by the retrieval of object-specific function knowledge.

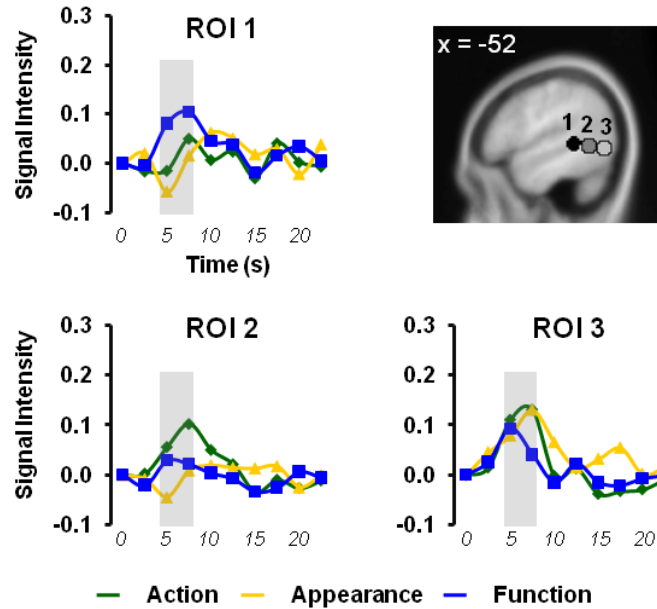


Figure 4.3. ROI localization and time series analyses in left pMTG. A description of the three ROIs is provided in the legend for Figure 2. To test for potential differences between conditions, we averaged intensity values across 5.0 and 7.5s, which largely captured the peaks across the conditions and ROIs (indicated by the shaded gray bar). *ROI 1* was more strongly engaged by Function than Action ($p < .05$) or Appearance ($p < .005$). *ROI 2* was more engaged by Action than Appearance ($p < .05$) or Function ($p < .05$). *ROI 3* exhibited no significant differences between the conditions ($F[2,28] < 1$). All reported coordinates are in MNI space.

pMTG ROI 2

In the first experiment, a region identified by acquiring the median coordinates to a subset of action knowledge studies (see Table 3.3) revealed greater engagement for the action/function knowledge conditions (Function, Imagery > Repeat, Rotate). In the present study, there was a significant difference between the time courses for the three conditions, $F(2,28) = 4.14$, $p = .027$, and this difference was driven by greater activation for the Action condition relative to Appearance and Function, $t(14) = 2.38$, $p = .032$ and $t(14) = 2.51$, $p = .025$, respectively (Figure 4.3 – ROI 2). In contrast to the previous findings, this region was most driven by accessing object-specific action knowledge.

pMTG ROI 3

In the first experiment, the ROI previously found to be sensitive to tool motion revealed an equal degree of activation across the conditions. In line with these findings, this region was equally engaged across our three task conditions in the present study, $F(2,28) < 1$ (Figure 4.3 – ROI 3).

Left VLPFC ROIs

In the previous study, both aVLPFC and pVLPFC were more engaged for both Function and Imagery relative to the control conditions, Repeat and Rotate. An examination of these regions in the present study revealed a difference between the time courses, $F(2,28) = 3.52$, $p = .043$, which was fueled by greater activation for Appearance than Function, $t(14) = 3.16$, $p = .007$, with Action intermediate to both (and not significantly different from either, $p > .10$). There was also a difference across the time courses in pVLPFC, $F(2,28) = 5.33$, $p = .011$. Action and

Appearance, which did not significantly differ from each ($p > .50$), were both more active than Function, $t(14) = 2.66, p = .019$ and $t(14) = 3.59, p = .003$, respectively. In sum, left VLPFC tended to be *least* engaged for Function, with greater activation for Appearance in aVLPFC and Action and Appearance in pVLPFC.

Discussion

In this study, we examined the role of left pMTG in supporting knowledge about the functions and actions associated with manipulable objects. Specifically, we sought to test whether left pMTG supports the representation of semantic function knowledge associated with a manipulable object function and/or the actions associated with it. We posited that if left pMTG represents function knowledge, this region should be most active when accessing conceptual knowledge about an object's function. In contrast, if this region represents action knowledge, it should be more active when retrieving knowledge about how to move your arm and hand when using the object.

We adapted our previous study (Chapter 3) to include three verbally-driven conditions that require semantic retrieval: (1) the purpose of the object (Function), (2) how you move your arms/hands when using the object (Action), or (3) the physical characteristics of the object (Appearance). In the same anterior-most ROI described above, activation was once again greatest for the Function condition (Figure 4.3: ROI 1). Self-reported difficulty ratings in our pilot experiment suggest that this effect cannot be explained by task difficulty.

A slightly more posterior region in left pMTG (ROI 2; -52 -54 0), centered on median coordinates from prior object knowledge studies (Table 3.3), revealed a markedly distinct profile of activation than ROI 1. In the first study, this ROI was modulated by both function and action knowledge, with greater activation for both Function and Imagery relative to the controls, Repeat and Rotate (Figure 3.2B: ROI 2). In this follow-up study, the ROI was most engaged by the Action condition, which required a description of the movements required during object use (Figure 4.3: ROI 2).

The ROI in posterior inferior temporal cortex (~BA 37) identified from two previous studies in which participants viewed moving tools (ROI 3; Table 3.3) did not discriminate between conditions in either experiment (Figure 3.2B: ROI 3; Figure 4.3: ROI 3). Rather, this region was engaged in a task-independent manner during the viewing of manipulable objects. Finally, a more superior region in posterior middle temporal cortex (BA 22/39) previously associated with biological motion (ROI 4; Table 3.3), was not significantly engaged in the first study (and therefore was not explored further in Experiment 2). In the present tasks, both ROIs 3-4 revealed no task-based modulation, as compared to the more anterior ROIs, ROIs 1-2.

In summary, the four adjacent ROIs in the posterior temporal lobe exhibited markedly different activation profiles. ROIs 1 and 2, but not the relatively more posterior temporal lobe ROIs, were engaged in a manner that was differentially modulated by the specific task demands, suggesting that these two ROIs may play different roles in supporting object action knowledge. It should be noted that although these four ROIs were analyzed separately, we view these data as being

indicative of an anterior-to-posterior gradient towards more specifically action-related activation in the more posterior extent of pMTG. This will be discussed further in Chapter 5.

With respect to VLPFC, previous work has implicated left aVLPFC (BA 45/47) in controlled, effortful retrieval of semantic information (Vandenberghe et al., 1996; Gabrieli et al., 1998; Wagner et al., 2001; Badre et al., 2005; Souza, Donohue & Bunge, 2009), and this implication has also extended to the tool knowledge literature (for review, Lewis, 2006). In the present study, we compared activation profiles for three conditions requiring semantic retrieval. In aVLPFC, activation was greatest for Appearance and weakest for Function, with Action intermediate to both. Because tools are primarily characterized by their functions, it is perhaps to be expected that activation in left aVLPFC is weakest for Function, which likely comes most naturally when thinking about tools. Appearance and Action, on the other hand, require an individual to consider aspects of the object that probably don't come quite as naturally as the object's function.

Left posterior VLPFC (BA 44/6) has been previously associated with selection of goal-relevant information (Thompson-Schill et al., 1997; Badre et al., 2005; Kan et al., 2006), verbal working memory (Gabrieli et al., 1998), as well as the representation of how tools can be used in a goal-directed manner (Johnson-Frey, Newman-Norlund & Grafton, 2005). In this study, we found that activation in pVLPFC was greater for both Action and Appearance than for Function trials. These findings could be interpreted as being consistent with a selection account, since the information to be retrieved in the Appearance and Action trials was, according to self-reports in the pilot study, less constrained than in the Function trials, which had straightforward answers. For example, there are a number of ways in which one could describe the features or actions associated with a stapler, but the primary function of a stapler is unambiguous.

In this study, we examined the nature of knowledge representations in left pMTG in the context of manipulable objects. After better controlling for task difficulty, we replicated the finding that a relatively anterior portion of left pMTG is involved in function semantics, while the more posterior regions showed sensitivity to action knowledge or no preference between the conditions. The findings are broadly consistent with the notion that although separate sub-regions of left pMTG show preferential engagement for certain types of knowledge, processing of this information is likely highly integrative and relies on other implicated regions for successful implementation of goal-directed behavior. These results lay the foundation for future research on the retrieval and implementation of action and function knowledge in the service of goal-directed behavior, which will be further reflected upon in Chapter 5.

Chapter 5

The current work sought to clarify the precise contributions of left VLPFC and left pMTG to goal-directed cognition. Each of these regions will be considered in turn.

Left VLPFC

In *Chapter 2*, we conducted an fMRI study that manipulated both controlled retrieval and selection demands in the context of foreign and domestic road sign meanings. Consistent with previous work (e.g., Badre et al., 2005), aVLPFC (BA 47) was most sensitive to controlled retrieval demands, while pVLPFC (BA 44/9) was most sensitive to selection demands. Interestingly, a region of mid-VLPFC (BA 44/9), which was anatomically intermediate to the aVLPFC and pVLPFC clusters, was sensitive to both manipulations, suggesting that this region could serve as an information integration zone.

The present findings extend those findings of a prior study on rule representation from our laboratory showing that left aVLPFC was sensitive to rule complexity during the presentation of verbal or non-verbal cues associated with task rules (Bunge et al., 2003). This region was sensitive to rule type during cue presentation, but not during the subsequent delay period, suggesting that it was involved in accessing meaning but not in guiding action. In contrast, left pVLPFC had exhibited rule sensitivity during both the cue and delay periods in the previous study, consistent with a role in representing rules as needed to guide action selection. These findings are consistent with a gradation of controlled retrieval and selection functions from anterior to posterior left VLPFC and potentially argue for a role of mid-VLPFC in serving as a conduit between these two regions.

In *Chapter 3*, we conducted an fMRI study design to examine the neural correlates of action and function knowledge using images of manipulable objects. Though the primary focus of this study was to investigate the nature of left pMTG activations during the viewing of manipulable objects, we also examined left VLPFC activity. Both left aVLPFC (BA 47) and pVLPFC (BA 44) were preferentially engaged during the retrieval of the object's intended function, such as the fact that a hammer is used to pound other objects. Interestingly, imagining using the object (Imagery) also significantly activated both sub-regions of left VLPFC more than mental rotation (Rotate) or repeating a prominent color name in the object (Repeat), though to a lesser extent than Function. The strong engagement for verbal semantic processing is consistent with prior work (Badre and Wagner, 2002; Demb, Desmond, Wagner, Vaidya, Glover et al., 1995; Gabrieli et al., 1998; Poldrack, Wagner, Prull, Desmond, Glover et al., 1999; Wagner, Pare-Blagoev, Clark & Poldrack, 2001), and the fact that this region is also active during motor imagery suggests that left VLPFC plays a role in the retrieval of both action and function knowledge associated with objects.

Finally, in *Chapter 4*, we conducted a follow-up fMRI study to address a limitation in the task design described in *Chapter 3*. We adapted the task design in Chapter 3, using an expanded set of object images and a modified set of experimental conditions. These conditions required participants to sub-vocally describe (1) the intended purpose of the object (Function), (2) the way in which one's arm(s)/hand(s) move when using the object (Action), or (3) the physical properties of the object, such as its color, shape, and component parts (Appearance). In left

aVLPFC, activation was greatest for Appearance, followed by Action and then Function. Because tools are primarily characterized by their functions, it is perhaps to be expected that activation in left aVLPFC is weakest for Function, which likely comes most naturally when thinking about tools. Appearance and Action, on the other hand, require an individual to consider aspects of the object that probably don't come quite as naturally as the object's function. In left pVLPFC, activation was greater for Action and Appearance relative to Function. These findings could be interpreted as being consistent with a selection account, since the information to be retrieved in the Appearance and Action trials was, according to self-reports in the pilot study, less constrained than in the Function trials, which had straightforward answers. For example, there are a number of ways in which one could describe the features or actions associated with a stapler, but the primary function of a stapler is unambiguous.

Collectively, these findings support the notion that left VLPFC guides the processing of knowledge that is relevant for guiding our interactions with the environment. It is quite likely that these sub-regions of left VLPFC, both aVLPFC and pVLPFC, fluidly interact, retrieving and selecting contextually relevant actions to guide our behavior.

Left pMTG

Our laboratory had previously found that left pMTG was engaged by road signs whose meaning was known relative to signs whose meaning was not known, but was insensitive to whether the signs were well-known or newly learned (Donohue et al., 2005). In our follow-up to this study (*Chapter 2*), we provided extensive training on sign meanings, thereby considerably reducing the error rate. Because we did not have sufficient statistical power to conduct this comparison, we identified left pMTG from a general condition comparing all conditions relative to fixation. As in our previous study (Donohue et al., 2005), we found that left pMTG – unlike aVLPFC and mid-VLPFC – was insensitive to controlled retrieval demands. We also found that this region was – unlike pVLPFC and mid-VLPFC – insensitive to selection demands. These findings are consistent with the idea that left pMTG stores action-relevant knowledge associated with visual stimuli (see also Bunge et al., 2003; Bunge, 2004), and that the effortful retrieval and selection of this knowledge may be mediated by the top-down control of left VLPFC over left pMTG.

In *Chapter 3*, we sought to further clarify the nature of the representations supported by left pMTG. Specifically, we aimed to better characterize the involvement of left pMTG when participants are viewing and considering properties about these objects. In an effort to bridge the findings from our first road sign study (Donohue et al., 2005) to the present study, we constructed a spherical ROI grounded in Donohue's left pMTG coordinates. Interestingly, activation in this ROI was driven by the retrieval of knowledge related to the functional purpose of the object. More posterior ROIs derived from coordinates from previous studies showed a different pattern of selectivity, with the next posterior ROI being sensitive to both action and function knowledge, and the most posterior ROI showing no preference across the conditions. These findings broadly support the notion that the more anterior region of left pMTG supports the representation of semantic knowledge associated with an object's function. However, a key limitation in the design, which was the possibility of the effect in left pMTG being driven by mere task difficulty and not the nature of the representations being accessed, weakened our ability to make stronger claims about this region.

The goal of *Chapter 4* was to attempt to replicate the left pMTG findings from *Chapter 3* while better controlling and accounting for task difficulty. Pre-fMRI piloting with a modified set of verbal conditions strongly supports the notion that the Function condition was not the most difficult condition. Again, activation in the spherical ROI pulled from Donohue et al. (2005) was strongest for the retrieval of semantic function knowledge, while the next posterior ROI showed preference to accessing knowledge about how the object moves when it is used. Collectively, work from *Chapters 2-4* suggest that the more anterior extent of left pMTG may more generally represent conceptual knowledge of how stimuli, not just objects, may be used (Bunge, 2004).

Future directions

An important issue to address in this field is the fact that many researchers studying cognitive control focus very little on the source of the accessed representations; likewise, researchers studying semantic memory representations focus very little on the neural mechanisms that bring them to mind. Given the incredible progress in biomedical technology that allows us to study the brain in more and more sophisticated ways, it is becoming increasingly important to study these processes as brain networks and systems. As such, as a field, we must strive to examine the dynamic interactions between brain regions that give rise to complex cognitive processes and memory representations.

To better test the hypothesis that left VLPFC guides controlled retrieval of semantic representations stored in posterior temporal cortex, we must be able to utilize causal methods. Transcranial magnetic stimulation (TMS) offers a powerful opportunity to test the integrity of this potential link. Despite some technical limitations (e.g., specificity of stimulated region), TMS and other similar methods should be used with increasing frequency to test the necessity of these regions in various cognitive processes.

Taken together, though we understand a good deal about left VLPFC and left pMTG function, there is still much to learn. With the use of more sophisticated techniques and analysis methods, the field of Cognitive Neuroscience is bound to lead us to even more important discoveries about how humans access and represent knowledge to guide our actions.

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