

Controlled retrieval and selection of action-relevant knowledge mediated by partially overlapping regions in left ventrolateral prefrontal cortex

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ABSTRACT

Information from long-term memory is used to identify appropriate responses to cues in the environment. Left ventrolateral prefrontal cortex (VLPFC) has been implicated in the effortful retrieval of semantic representations, as well as in the goal-directed selection between such representations. It has also been suggested that left posterior middle temporal gyrus (pMTG) stores the rules which VLPFC accesses to guide behavior. In the present event-related fMRI study, we examined the contributions of left VLPFC and pMTG in the controlled retrieval and selection of action-relevant knowledge associated with road signs. Controlled retrieval demands were manipulated by varying how recently the sign meaning was learned, and selection demands were manipulated by varying the number of competing meanings associated with a sign.

Activation in anterior VLPFC was consistent with controlled retrieval, activation in posterior VLPFC was consistent with selection, and activation in mid-VLPFC was sensitive to both manipulations. Left pMTG, while active, was not sensitive to these manipulations. These findings highlight the role of left VLPFC in accessing and maintaining goal-relevant information for the control of action.

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Introduction

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 et al., 2000; Passingham et al., 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 et al., 2005; Bussey et al., 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 et al., 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 et al., 2003; Crone et al., 2006; Donohue et al., 2008).

In humans, it is well-known that left VLPFC plays a critical role in language production and comprehension (Gabrieli et al., 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 et al., 1995; Gabrieli et al., 1998; Poldrack et al., 1999; Wagner et al., 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 et al., 2007; Wagner et al., 1997, 2001). An alternate idea, known as the selection hypothesis, contends that the role of left VLPFC is to select goal-relevant information from competing representations (Kan et al., 2006; Kan and Thompson-Schill, 2004; Persson et al., 2004; Thompson-Schill et al., 1997, 1999). Though in some cases manipulations of controlled retrieval can be bound to changes in selection (for discussion, Thompson-Schill et al., 2005), it is possible to manipulate controlled retrieval and selection demands separately, as selection is thought to operate post-retrieval (for review, Badre and Wagner, 2002).

Data from Badre et al., using a paradigm with materials modified from Wagner et al. (2001), used factor analysis to examine whether controlled retrieval and selection can be reduced to one putative

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cognitive process. 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) (Badre et al., 2005). Many of the aforementioned studies involved variants of a task in which participants must select a response from among a set of words. Here, 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 et al., 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 et al., 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).

The task included four conditions: Old, New, Re-Old, and Re-New (Fig. 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

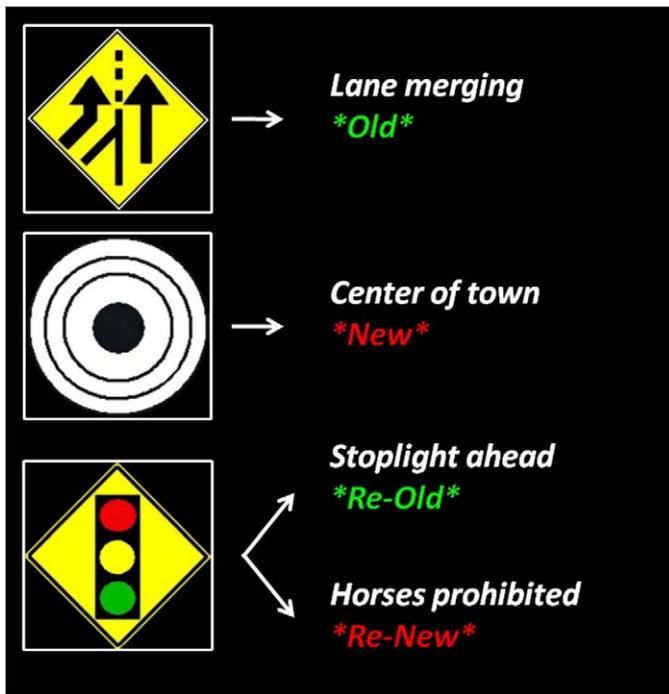


Fig. 1. Experimental conditions. The present study manipulated controlled retrieval and selection demands by varying when a sign meaning was learned (old, new) and how many meanings a sign possessed (one, two). “Old” referred to domestic signs with their original meaning, “New” referred to foreign road 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.

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 giving 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 2.5 s and 7.5 s, 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 et al., 1997), an approximation of Talairach space (Talairach and Tournoux, 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 et al., 2002; <http://marsbar.sourceforge.net/>). 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 active after a false discovery rate (FDR; Genovese et al., 2002) corrected threshold of $p < .05$, with a 10-voxel extent. See Supplementary 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.

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, ($F < 1$; Fig. 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 (Fig. 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 Fig. 3.

Fig. 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

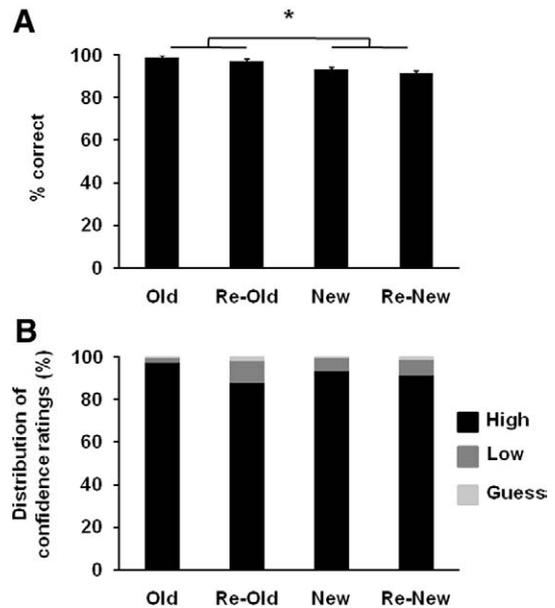


Fig. 2. Post-scan behavioral results. (A) Data from the post-scan test indicate that although accuracy was high for all conditions (>90%), participants correctly recalled the old items (Old, Re-Old) with greater frequency than new items (New, Re-New). The lack of a Knowledge \times Number of Meanings 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.

with two meanings. Fig. 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 (Fig. 2A). Mirroring this pattern of results, Fig. 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, Fig. 3D represents this potential activation pattern, with activation in the Old condition reduced relative to the other conditions. In contrast to Fig. 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

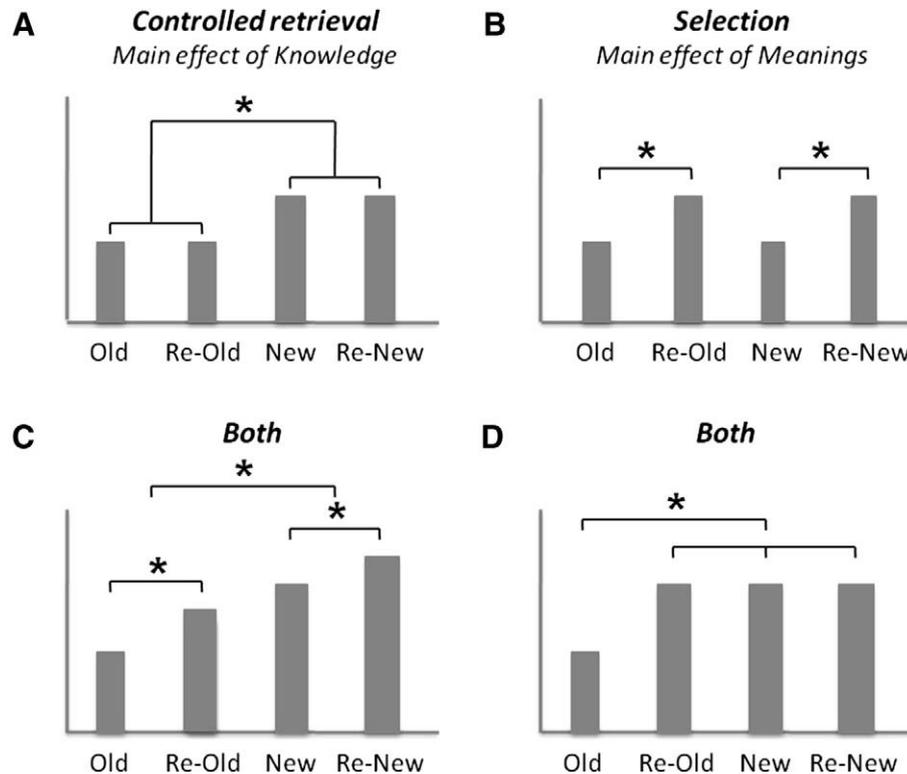


Fig. 3. Predicted profiles of brain activation for regions involved in controlled retrieval and/or selection. Y-axis values are arbitrary, and correspond to hypothetical contrast values. (A) The pattern that a pure controlled retrieval region would exhibit. This region would be exclusively driven by 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 A, 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 \times 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 B, where confidence ratings were highest for Old meanings, and relatively reduced for Re-Old, New, and Re-New.

one in right VLPFC (center of mass = 54 30 27; 61 voxels) (Fig. 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 (Fig. 4A), the magnitude and profile of activation were 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 Fig. 3D.

Dissociable activation profiles within left VLPFC

The large cluster in left VLPFC (Fig. 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 (Fig. 3). To identify regions specifically involved in controlled retrieval (Fig. 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 (Fig. 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 (Figs. 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 (Figs. 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

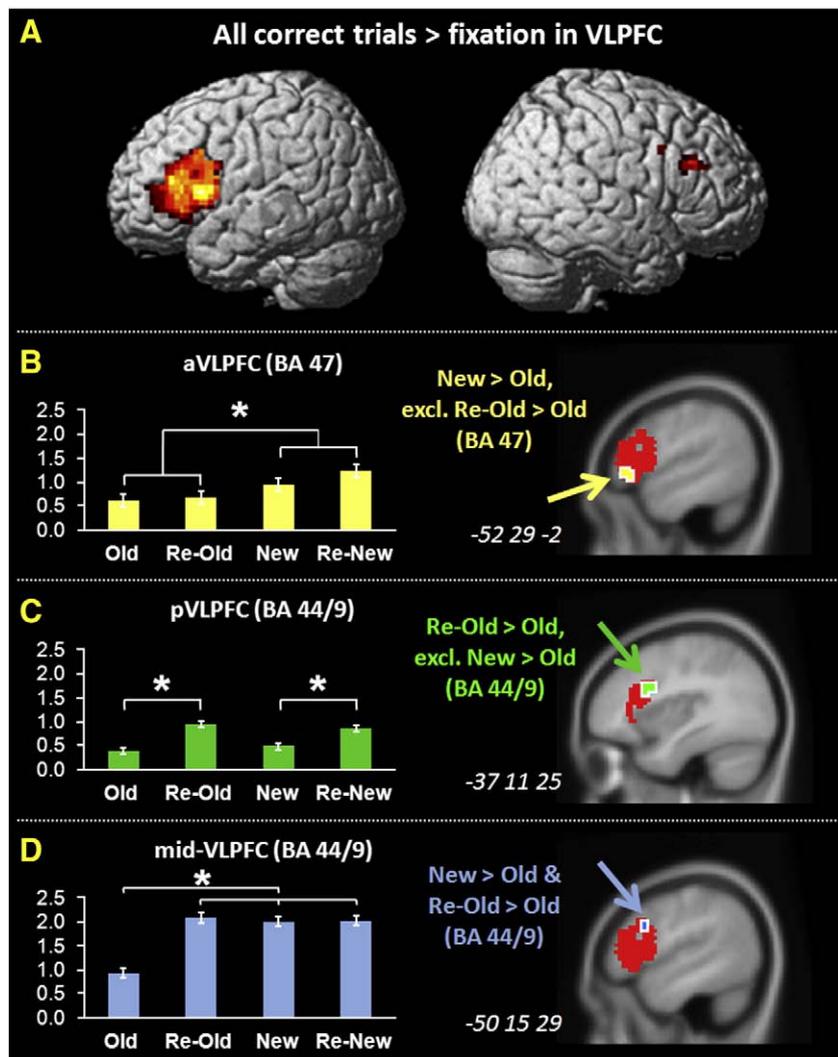


Fig. 4. Left VLPFC activation and ROI analyses. (A) Group contrast of all correct sign meaning retrievals relative to fixation, anatomically constrained to left and right VLPFC only ($p < .05$, corrected for multiple comparisons using false discovery rate (FDR), with a minimum ten voxel extent threshold, 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 Fig. 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 Supplemental Fig. 1A 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 Fig. 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 Supplemental Fig. 1B 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 Fig. 3D. Brodmann areas cited for each region are approximations based on the Talairach atlas (Talairach and Tourneaux, 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.

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 (Figs. 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; $[-52\ 29\ -2]$; Fig. 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 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 aVLPFC to the first presentation of a sign (see [Supplemental Fig. 1A](#) for the activation profile associated with the second presentation). A Knowledge (old, new) \times Meanings (1, 2) repeated measures ANOVA revealed that aVLPFC 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*, $F(1,12) < 1$) ([Fig. 4B](#) – left). This pattern observed in left aVLPFC is consistent with a role in controlled retrieval, as in the hypothetical plot in [Fig. 3A](#).

The pVLPFC cluster (BA 44/9; $[-37\ 11\ 25]$; [Fig. 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 pVLPFC to the first presentation of a sign (see [Supplemental Fig. 1B](#) 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*, $F(1,12) = 2.22$, $p = .16$) ([Fig. 4C](#) – left). This pattern in left pVLPFC is consistent with a role in selection, as in the hypothetical plot in [Fig. 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 [Figs. 3C, D](#). We identified a cluster of activation in mid-VLPFC (BA 44/9; $[-50\ 15\ 29]$; [Fig. 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, $F(1,12) = 29.12$, $p < .001$ ([Fig. 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 et al., 2004](#)).

In the present study, a region within the “cognitive” division of the ACC ([Bush et al., 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 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 VLPFC 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 ([Fig. 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 Fig. 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. 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 et al. reported (−51 27 −3) as being most affected a manipulation of associative strength. 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, and is consistent with other studies implicating this region in selection (Kan and Thompson-Schill, 2004; Thompson-Schill et al., 1997, 1999). Finally, our mid-VLPFC cluster (−50 15 29) showed sensitivity to both controlled retrieval and selection manipulations. Thus, as proposed by Badre et al. (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 present findings extend the 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.

We had previously found that left pMTG was engaged by signs whose meaning was known relative to signs whose meaning was not known, but was insensitive to whether the signs were old or new (Donohue et al., 2005). In our current study, the sign meanings were all well-learned, and we did not have enough trials to compare signs whose meanings the subjects did versus did not remember in the post-scan test. 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 is mediated by the top-down control of various regions in left VLPFC over left pMTG. A technique with higher temporal resolution is required to further test our ideas regarding the contributions of various brain regions to rule retrieval and selection (see Bunge, 2004, and Bunge et al., 2005).

Conclusion

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. 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. As a whole, these subregions of left VLPFC fluidly interact, retrieving and selecting contextually relevant actions to guide our behavior. Further research

at work at the intersection of long-term memory and cognitive control, like this study, promises to shed new insights into the mechanisms by which we decide how to behave.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.01.046.

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