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Retrieving rules for behavior from long-term memory

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Human behavior is often dictated by rules or prescribed guides for action. Little is currently known regarding how these rules are stored in long-term memory or retrieved and implemented. Here, we examined the roles of ventrolateral prefrontal cortex (VLPFC) and posterior middle temporal gyrus (postMTG) in rule use. We tested two hypotheses: first, that knowledge about actions associated with abstract visual symbols is stored in postMTG, and second, that VLPFC is involved in the controlled retrieval of rule meanings. Subjects viewed a series of road signs during event-related fMRI data collection. Three types of signs were intermixed: highly familiar signs, novel signs whose meaning was explained to subjects prior to scanning, and novel signs whose meaning was not explained. Subjects were asked to think about the meaning of each sign as it was presented during scanning and then to give its meaning in a post-scan test. Left postMTG was more active when subjects viewed signs whose meaning they knew than signs whose meaning they did not know, consistent with a role in storing rule meanings. This region was not modulated by experience, in that it was equally engaged by newly trained and well-learned signs. In contrast, right VLPFC was more active for newly trained signs than for either well-learned or incorrect ones, consistent with a role in controlled retrieval. Left VLPFC was reliably engaged while subjects attempted to interpret the signs but did not differ according to knowledge or experience. These data implicate postMTG in rule storage and VLPFC in rule retrieval.

Keywords: Long-term memory; Human behavior; Rule retrieval; Action; Control; Rules; Cognitive

Introduction

The decision of how to behave under a particular set of circumstances is facilitated by the ability to draw on relevant rules, or “prescribed guide[s] for conduct or action” (The Merriam-Webster Dictionary, 1974). Such rules range from simple stimulus–response associations that are explicitly learned to implicit guidelines for social interactions. Meaningful behavior often depends on the ability to retrieve and use the right rule at the right time. Consequently, a detailed account of how we use rules to make decisions would constitute an important advance in our understanding of human behavior.

Thus far, neuroscientific research on rule use in humans and other animals has focused primarily on how rules are learned, maintained online, and implemented (for reviews, see Bunge, 2004; Murray et al., 2000; Passingham et al., 2000). These studies have consistently implicated prefrontal cortex (PFC), and in particular, ventrolateral PFC (VLPFC), in the ability to learn and implement rules (Bussey et al., 2001; Passingham et al., 2000). An important question about rule use that has yet to be addressed is: where and how are rules for behavior stored in the brain? PFC is an unlikely long-term repository of rule knowledge, in part because patients with PFC damage can carry out the basic tasks of their daily lives quite well, as long as they can rely on well-learned rules (Shallice and Burgess, 1991). A likelier candidate is lateral temporal cortex, which both neuropsychological and brain imaging studies have implicated in the storage of semantic knowledge (Damasio et al., 1990, 2001; Hillis and Caramazza, 1991; Hodges et al., 1992, 2000; Gerlach et al., 2000; Grossman et al., 2002; Mummery et al., 1996, 2000; Phillips et al., 2002; Tranel et al., 2001).

The first goal of the current fMRI study was to test the hypothesis that rule knowledge is stored long-term in a specific portion of the temporal lobes that has previously been hypothesized to store action knowledge (Chao et al., 1999). The second goal was to determine the extent to which PFC would be recruited during retrieval of both well-learned and recently learned rules. In effect, the finding that PFC patients can operate on the basis of well-learned rules does not necessarily mean that PFC is not typically involved in retrieving these rules. We sought to explicitly test the hypothesis that PFC is more strongly engaged during retrieval of recently learned rules than well-learned ones.

In a prior fMRI study focusing on rule retrieval and maintenance (Bunge et al., 2003), we observed activation of left posterior middle temporal gyrus (postMTG), as well as several regions in left PFC, when subjects viewed instructional cues that were associated with specific rules. This cue-period activation in postMTG and PFC was sensitive to rule complexity, suggesting that PFC–in particular, left anterior VLPFC–might retrieve rule knowledge from postMTG. These regions were not strongly active during the delay and did not differentiate between rule type. In

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contrast, posterior VLPFC and parietal cortex, regions implicated in verbal working memory, were implicated in rule maintenance over the delay. These results suggest that there are dissociable neural networks for rule retrieval and rule maintenance and tentatively implicate postMTG in long-term rule storage.

The left postMTG focus from our prior study (Bunge et al., 2003) was close to a region that Alex Martin, Linda Chao, and others have characterized as representing knowledge about actions associated with manipulable objects (Beauchamp et al., 2002; Chao et al., 1999; Johnson-Frey, 2004; Martin and Chao, 2001; Tyler et al., 2003; see also Bunge, 2004). Left postMTG is active when subjects generate action verbs (Damasio et al., 1996; Kable et al., 2002), mentally conceptualize the physical gestures associated with tool use (Johnson-Frey et al., 2004), and make judgments about manipulable objects (Kellenbach et al., 2003). Taken together with our prior data, this constellation of results raises the possibility that postMTG stores a variety of different kinds of action knowledge, ranging from non-arbitrary associations between real-world objects and specific actions to completely arbitrary associations between symbols and associated rules. We sought to further test this hypothesis in the present study.

As noted above, VLPFC has been implicated in rule retrieval (Brass and von Cramon, 2004; Brass et al., 2003; Bunge et al., 2003; Toni and Passingham, 1999; Toni et al., 1998, 2001). This region is thought to be important for active memory retrieval under situations in which relevant associations do not spring readily to mind—i.e., when relations between representations are weak, unstable, or ambiguous (Petrides, 2002; see also Miller and Cohen, 2001). Animal studies indicate that VLPFC retrieves information from the temporal lobes (Eacott and Gaffan, 1992; Hasegawa et al., 1999; Miyashita and Hayashi, 2000; Petrides, 1996). In human fMRI studies, left anterior VLPFC has been implicated in semantic memory retrieval (Gabrieli et al., 1998; Poldrack et al., 1999; Wagner et al., 2001). This region is more active when subjects retrieve weaker semantic associations between words (e.g., apple–teacher) than stronger ones (e.g., apple–fruit), suggesting that it is associated with *controlled* rather than automatic retrieval (Wagner et al., 2001). We have previously hypothesized that VLPFC has an inverted-U relationship with associative memory strength (Bunge et al., 2004). According to this hypothesis, VLPFC is recruited when subjects engage retrieval processes that lead to the successful recollection of knowledge, and more so when recollection is effortful (Wagner et al., 2001). However, under situations in which initial recollection attempts are unsuccessful and subjects abandon the retrieval effort, one might then observe diminished reliance on VLPFC processes (see also Dobbins et al., 2003). Thus, the inverted-U model predicts greatest activation in VLPFC during effortful recollection relative to less effortful recollection or abandonment of an early retrieval attempt. We sought to test this hypothesis by comparing VLPFC activation during rule retrieval across three levels of memory strength.

The current study was designed to explicitly test our hypotheses about postMTG and VLPFC contributions to long-term rule storage and controlled rule retrieval, respectively. To this end, whole-brain fMRI data were acquired, while subjects viewed various road signs from around the world. Road signs were selected for two reasons: first, because they are associated with specific actions or with guidelines that can be used to select specific actions, and second, because they presented the opportunity to examine retrieval of knowledge about familiar signs from remote long-term memory. Included in the study were 'Old' signs that subjects had used while driving for at least 4 years, and 'New' signs from other countries that they were unlikely to have been exposed to previously. Of these New signs, half were 'Trained': that is, subjects were told their meaning prior to scanning but had had no experience using them to guide their actions. The other half of the new signs were 'Untrained'—in other words, subjects had viewed them prior to scanning but were not given their meaning.

We sought to gauge the level of involvement of PFC in retrieval of well-learned sign meanings, independent of PFC activation during response selection. To this end, subjects had no response requirements during scanning but were merely asked to think about the meaning of each road sign. After scanning, we probed subjects for the meaning of each sign. This post-scan memory test allowed us to separate trials associated with signs that subjects knew or did not know the meaning of (correct vs. incorrect). We predicted that postMTG would be active when subjects successfully accessed the meaning of Old and Trained signs, but not when subjects viewed signs whose meaning they did not know (incorrect trials, of which the majority would be Untrained). We further predicted that VLPFC would exhibit an inverted-U function with respect to strength of rule knowledge (correct Trained > correct Old, incorrect).

Methods

Subjects

Paid volunteers were recruited from the University of California at Davis. Fourteen healthy, right-handed volunteers were included in this study (9 females, 5 males; 20–30 years old, mean age = 23.3). Three additional subjects were excluded: two on the basis of equipment malfunction during data acquisition and one on the basis of excessive motion. All subjects had been driving for more than 4 years, and none had ever driven outside of the United States. Informed consent was obtained from all subjects, and all procedures were approved by the Internal Review Board at UC Davis.

Stimuli

A survey administered to 20 U.S. drivers was used to select appropriate stimuli for the study. This survey included 150 road signs from the US and around the world, and the respondents were asked for the meaning of each sign. A group of 44 domestic (U.S.) signs that were correctly identified by more than 70% of the respondents were classified as Old. Additionally, a group of 90 foreign signs and obscure domestic signs whose meaning was correctly identified by fewer than 30% of respondents were classified as New. All 44 Old and 88 of the New stimuli were included in the experiment, with the expectation that subjects would be familiar with a majority of the Old stimuli and a minority of the New ones. Half (44) of the New stimuli were assigned to the Trained condition because subjects would be taught their meaning. The other 44 New signs were assigned to the Untrained condition. These assignments were counterbalanced across subjects. Where possible, signs that did not contain any text were selected for the experiment. For signs containing text, the words were blurred so that subjects would be unable to read them. The blurring was done in such a way as to simulate how text on a sign might be perceived from a distance.

Experimental procedure

In a pre-scan training session, subjects began by viewing each Old, Trained, and Untrained sign for 500 ms, with signs from the different conditions randomly intermixed. The purpose of this initial viewing period was to familiarize subjects with all the visual stimuli. Next, subjects were taught the meaning of half of the New signs. Each of the signs in this Trained condition was viewed 4 times for 4 s, while the experimenter explained the meaning.

During scanning, subjects viewed Old, Trained, and Untrained signs for 5 s each in an event-related design (Fig. 1). They performed a total of 132 experimental trials over the course of two 7.5-min fMRI scans. The order of trials within each 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). Periods of visual fixation lasting between 2.5 and 7.5 s, jittered in increments of 2.5 s, were interleaved with the experimental trials as determined by the optimization algorithm.

After scanning, subjects were shown all of the signs again, in the same order as in the scanner. As each sign appeared on the screen, subjects pressed one of three buttons to indicate how confident they were of the meaning (High confidence/Low confidence/Guess). They were instructed to respond as soon as they had made their choice, and their response times (RTs) for these judgments were recorded. After indicating their confidence rating for a sign, subjects were asked to explain the meaning of the sign to the experimenter. Verbal responses were documented and were later scored for accuracy. Subjects then pressed the space bar to proceed to the next trial.

fMRI data acquisition

Scanning was performed on a 1.5 T 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. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2.5 s, TE = 40 ms, 35 axial slices, 3.44 × 3.44 × 3 mm, 0.5 mm inter-slice gap, 180 volumes per run). Prior to each scan, four volumes were discarded to allow for T1-equilibration effects. High-resolution T1-weighted coronal anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head.

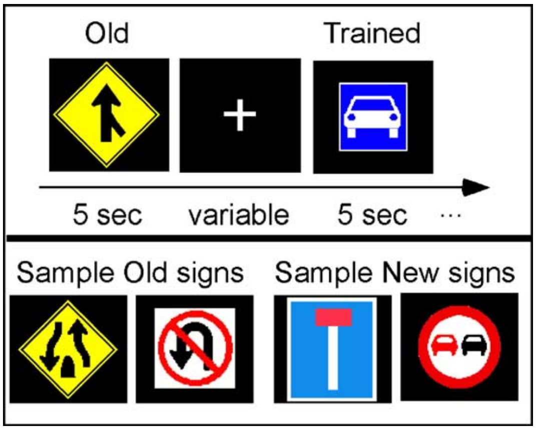

Fig. 1. Event-related fMRI design. During scanning, subjects were shown the Old, Trained, and Untrained road signs for 5 s each, with a variable–duration fixation cross-hair interspersed between each sign. Subjects were asked to "think about the meaning" of each sign, and no response was required. Examples of Old and New stimuli are presented here. All stimuli used in the experiment are available upon request.

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 were then submitted to rigid body motion correction with sinc interpolation. Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. Templates are based on the MNI305 stereotaxic space (Cocosco et al., 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 2 × 2 × 2 mm cubic voxels. Functional volumes were spatially smoothed with 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). 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 subject-by-subject basis, were submitted to group analyses. Incorrect trials 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 subjects as a random effect. Task-related responses during the cue and delay periods were considered significant if they consisted of at least 5 contiguous voxels that exceeded an uncorrected threshold of $P < 0.001$.

Region-of-interest (ROI) analyses were performed with the MarsBar toolbox in SPM2 (Brett et al., 2002; http://marsbar.sourceforge.net/). The purpose of these analyses was to further characterize the activation profiles of temporal and prefrontal regions identified in one or more contrasts (correct > incorrect, or Trained > Old). ROIs that spanned several functional brain regions were subdivided by sequentially masking the functional ROI with each of several MarsBar anatomical ROIs. Mean contrast values for each subject and condition were extracted for each ROI and submitted to ANOVAs and post hoc comparisons. Adjusted peristimulus time-course data were extracted for each scan and condition and averaged across scans and subjects using a Marsbar-compatible custom MATLAB script for use with SPM2 data (Carter Wendelken).

Results

Behavioral data

Accuracy was measured as the percentage of signs from a given condition that subjects could accurately give the meaning of during the post-scan session (i.e., ‘correct’ trials) (Fig. 2A). RTs were measured as the latency with which subjects made a confidence judgment after a sign appeared on the screen (Fig. 2B). Mean accuracy and RT differed significantly across conditions ($F(2,26) = 254.3$; $P < 0.0001$; $F(2,26) = 18.0$; $P < 0.0001$). Post hoc comparisons indicated that subjects were more accurate on Old than Trained signs ($F(1,13) = 6.1$; $P < 0.025$) but that RTs associated with the confidence judgment did not differ between Old and Trained conditions ($F < 1$). Subjects responded more quickly and accurately to Old and Trained than Untrained signs (Trained vs. Untrained accuracy: $F(1,13) = 330.5$; $P < 0.0001$; RTs: $F(2,26) = 23.9$; $P < 0.0001$).

To investigate the basis for subjects’ responses in the post-scan session, we measured the proportion of High confidence, Low confidence, and Guess judgments associated with correct responses in each condition (Fig. 2C). A 3 × 3 ANOVA with within-subject factors of Confidence (High, Low, Guess) and Condition (Old, Trained, and Untrained) demonstrated a significant Confidence × Condition interaction ($F(4,48) = 65.3$; $P < 0.0001$). Subjects were highly confident on a greater proportion of correctly performed Old than Untrained trials ($F(1,48) = 88.4$; $P < 0.0001$)). There was a tendency for subjects to report that they were highly confident more often for Trained than Old signs, although this effect was not significant ($F(1,48) = 3.0$; $P > 0.05$). Thus, as expected, subjects were more accurate and confident when giving the meaning of Old and Trained signs than Untrained signs. Because there were very few correct Untrained trials (and these tended to be judged by the subjects as guesses), the fMRI analyses focused exclusively on comparisons between correct Old, correct Trained, and incorrect trials.

It is important to note that the behavioral results were obtained after scanning rather than while subjects viewed the signs in the scanner. Thus, these behavioral indices may not be a perfect indicator of whether subjects knew the signs’ meanings during scanning. In particular, it is possible that subjects were better able to retrieve meaning for the Trained signs upon viewing them again during the post-scan test. Our initial behavioral pilot data seem to suggest otherwise, in that subjects who performed the post-scan test were no more accurate than were the behavioral pilot subjects who had to explain sign meanings upon first viewing them (80% mean accuracy for both groups). Moreover, any tendency towards better recollection in the post-scan test than during scanning would serve only to *diminish* our ability to detect the hypothesized neural differences (for correct vs. incorrect and correct Trained vs. correct Old trials) when sorting trials on the basis of post-scan accuracy.

Retrieval success effects

To characterize regions associated with rule knowledge, we compared whole-brain activation for correct vs. incorrect signs (Fig. 3A, Table 1). As predicted, left postMTG (Brodmann area [BA] 21) was the region most strongly modulated by this comparison. Several additional regions in the temporal lobes were more active when subjects viewed signs whose meaning they knew, including more anterior regions in bilateral middle temporal gyrus (BA 21), left inferior temporal gyrus (BA 20), and right superior temporal gyrus (BA 38). Left hippocampus and parahippocampal gyrus (medial temporal lobe; MTL) and right motor cortex (BA 4) were also identified by this contrast.

Controlled vs. automatic retrieval

To identify regions that were more active during controlled than relatively automatic retrieval of meaning, we compared correct Trained and correct Old trials (Fig. 3B; Table 1). We had predicted VLPFC activation for this contrast, and indeed found that right VLPFC (BA 11/47) was engaged more strongly for Trained than Old trials. Other activations were observed in right DLPFC (BA 8/9 and 9/10), as well as in left PMv and pre-SMA (BA 6).

Activation associated with “passive” viewing of road signs

In addition to these directed contrasts, we performed a general contrast to identify all the regions that were active while subjects viewed images of road signs (Fig. 3C; Supplementary Table). This contrast identified a number of regions, including left anterior and posterior VLPFC (BA 45 and 44), right DLPFC (BA 46), left fusiform gyrus (BA 37), left middle temporal gyrus (BA 21), right MTL (BA 36), left pre-SMA (BA 6), left superior parietal lobule (BA 7), and right motor cortex (BA 4). A similar set of activations was observed in the comparison of correct trials relative to fixation, except that the area of activation extended anterior and dorsal to that seen in the left middle temporal cortex for All Conditions > fixation (Supplementary Table). A region-of-interest (ROI) analysis of left anterior VLPFC confirmed that this region was indiscriminately engaged during viewing of Old, Trained, and incorrect signs (Fig. 4A).

ROI analyses based on directed contrasts

ROIs obtained from the contrast of correct > incorrect trials were further analyzed to determine whether these regions–shown

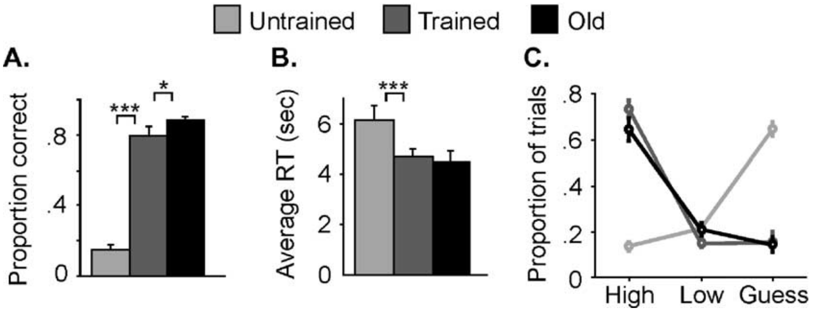

Fig. 2. Behavioral data from the post-scan session. Plots of accuracy, RT, and confidence ratings across all subjects ($N = 14$). Confidence ratings and RTs are shown for correct responses only. Subjects were more accurate, faster, and more confident when providing meanings for the Old and Trained signs than for the Untrained signs.

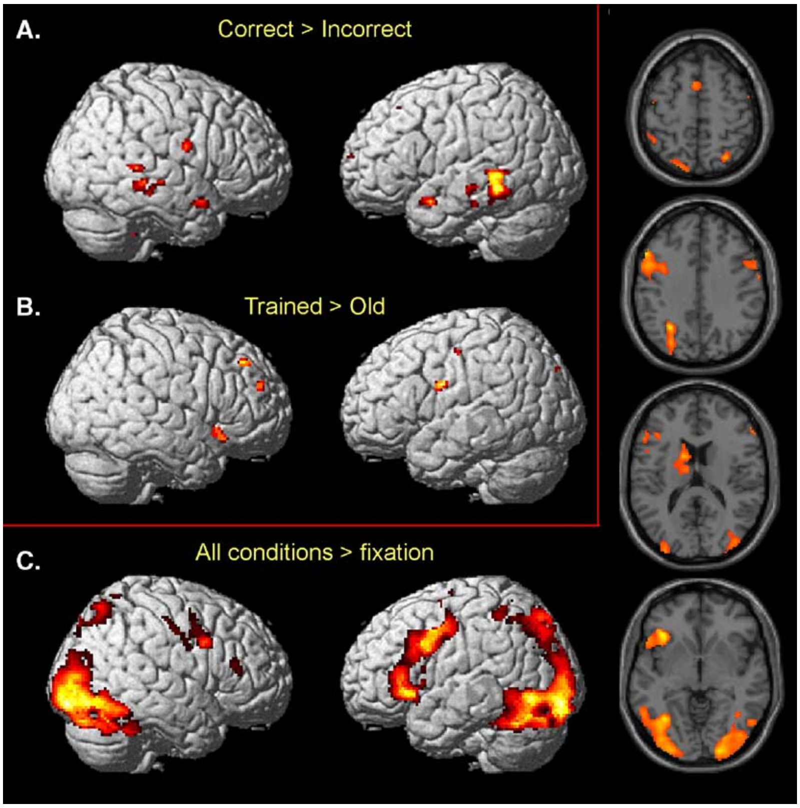

Fig. 3. Group-averaged activations. (A) Displayed here are regions that were more active while subjects viewed signs whose meaning they knew than signs that they did not know. Activation is observed in bilateral MTG (BA 21/38) and right motor cortex (BA 4). (B) Displayed here are regions that were more active while subjects viewed Trained than Old signs. This contrast was limited to signs that subjects correctly identified. Activation is observed in right VLPFC (BA 47) and DLPFC (BA 9/10, BA 8/9), left ventral premotor (BA 6), and left postcentral gyrus (BA 3). (C) Activation across all conditions relative to fixation, depicted in both 3D-renderings and axial slices. From top to bottom, the slices correspond to z coordinates of 55, 35, 15, and −5. Activation is observed in (1) left pre-SMA (BA 6), (2) left anterior inferior parietal lobule (BA 40), (3) bilateral superior parietal lobule (BA 7) (top slice); (4) left DLPFC (BA 9), (5) right VLPFC (BA 44), (6) left precuneus (BA 19) (second slice); (7) left VLPFC (BA 45), (8) left caudate, (9) right DLPFC (BA 46), (10) bilateral peristriate cortex (BA 19) (third slice); (11) left VLPFC (BA 47), and (12) bilateral peristriate cortex (BA 19) (bottom slice). All contrasts are displayed at a voxel-threshold of $P < 0.001$, with an extent threshold of 5 voxels. Contrasts shown in the inset (A and B) are masked to exclude deactivations (regions activated by fixation > all conditions at $P < 0.05$ uncorrected).

to be sensitive to retrieval success–were also sensitive to experience (Trained vs. Old). Five foci were identified from this contrast within the left middle temporal gyrus (BA 21) and right superior and middle temporal gyri (BA 21/22). None of these ROIs differed significantly between Old and Trained signs (all $P > 0.10$). In contrast to lateral temporal cortex, a region in the left anterior MTL was found to be significantly more active for Old than Trained signs ($F(1,13) = 7.7$; $P < 0.02$). An ANOVA confirmed that this left MTL ROI had a different profile of activation from the large cluster in left postMTG (Fig. 5). This result indicates that left postMTG was preferentially engaged when the meaning of a sign was known, whereas left anterior MTL was preferentially engaged when subjects viewed signs that they had encountered numerous times outside of the laboratory setting.

Conversely, ROI analyses were performed to examine whether the regions that were more active for Trained than Old trials were modulated by retrieval success (correct vs. incorrect). ROI analyses focused on regions in right anterior VLPFC, as well as right DLPFC, left PMv, and left pre-SMA. Right VLPFC displayed the predicted pattern, in that it was preferentially engaged by the Trained signs relative to both Old and incorrect signs (Fig. 4B). The time-series analysis revealed a deactivation for Old signs relative to fixation, whereas the response to the incorrect signs appeared quite variable. The pattern displayed by right DLPFC (Fig. 4C) did not differ significantly from that of right VLPFC ($F < 1$ for VLPFC vs. both DLPFC ROIs). Left pre-SMA differed from right VLPFC ($F(2,26) = 3.6$; $P < 0.05$) in that it did not significantly differ between Trained and incorrect signs ($F(1,13) = 2.4$; $P > 0.10$). Although left PMv was more active for Trained than Old and incorrect signs, like left pre-SMA, it did not significantly differ between the Trained and incorrect signs ($F(1,13) = 2.6$; $P > 0.10$). In summary, right VLPFC and DLPFC showed an inverted-U pattern as a function of memory strength, and qualitatively similar but non-significant functions were observed for left PMv and pre-SMA.

Testing the effect of arbitrariness

Rule retrieval is easier when a symbol is non-arbitrarily associated with the rule (e.g., an arrow pointing to the left) than when the association is arbitrary (e.g., an inverted yellow triangle). We were interested in determining whether our fMRI results could be explained by differences in arbitrariness of the stimuli in each condition. Differences between Trained and Untrained signs should not be affected by arbitrariness, because the New signs assigned to these conditions were counterbalanced across subjects. However, it

Table 1
Activation foci for directed contrasts of interest

Region of activation	BA	*x*	*y*	*z*	*Z* score	Volume (mm^3)
Correct > incorrect signs						
Inferior temporal gyrus	L20	−60	−26	−20	3.6	88
Middle temporal gyrus	L21	−62	−46	−10	4.22	–
	L21	−56	−40	2	4.37	2728
	L21	−48	6	−18	4.33	408
	L21	−52	−22	−10	3.61	200
	R21	48	−26	−6	3.68	232
Superior temporal gyrus	R22	66	−42	8	3.65	160
	R22	52	−36	6	3.48	160
	R38	50	10	−20	3.43	352
Parahippocampal gyrus/hippocampus	L35	−20	−10	−24	4.1	160
Posterior cingulate	L31/23	−6	−56	24	3.84	952
Medial frontal gyrus	L10	−6	64	14	3.37	56
Medial frontal gyrus	R6	10	−10	54	3.33	56
Precentral gyrus	R4	62	−4	22	4.17	328
Superior frontal gyrus	L10	−12	54	−2	3.17	472
Superior frontal gyrus	L8	−18	30	50	3.31	40
Cerebellar tonsil	R	32	−40	−42	3.17	56
Correct Trained > correct Old signs						
Inferior frontal gyrus	R11	14	24	−16	4.15	200
Inferior frontal gyrus	R47/11	34	24	−14	3.45	416
pre-SMA	L6	−10	6	50	3.8	152
Middle frontal gyrus	R8	40	38	42	3.63	248
PMv	L6	−60	0	26	4.09	376
Superior frontal gyrus	R9/10	40	50	26	3.41	200
Precuneus	L19	−12	−84	38	3.8	512
Postcentral gyrus	L3	−54	−14	50	3.29	56
Cingulate gyrus						
Cingulate gyrus	L24	−8	−8	34	3.29	112
Cingulate gyrus	L31	−2	−40	30	3.61	880
Cingulate gyrus	R32	6	16	30	3.28	
Cingulate gyrus	R32	12	20	38	3.25	
Correct Old > correct Trained signs						
Middle frontal gyrus	R9	60	20	28	3.58	112
Cuneus	L18	−28	−96	2	3.48	64

was possible that systematic differences in arbitrariness could contribute to differences between the Old trials and the other trial types.

Although the signs were not pre-selected according to this dimension, we had 5 independent raters decide whether each sign was arbitrary or non-arbitrary, and we then classified it on the basis of the most common response (3 or more out of 5). There was some disagreement between the raters; indeed, this rating is somewhat subjective, and accordingly, we had predicted that unfamiliar signs would be more likely to be rated as arbitrary than familiar signs. Based on this pilot sample, 40% of the Old signs and 69% of the New signs were judged to be arbitrary. We then reran the fMRI analyses for the data reported here, subdividing signs according to whether they were arbitrary, non-arbitrary, or incorrect. ROI analyses were performed for the regions in the MTG, MTL, pre-SMA, DLPFC, VLPFC, and PMv discussed above. None of these ROIs were modulated by arbitrariness except for PMv. This region was more active for arbitrary than non-arbitrary signs (1.13 vs. 0.285; $F(1,13) = 10.483$; $P < 0.01$), which is most likely related to the fact that it was more active for Trained than Old signs. These data suggest that PMv is involved in the effortful retrieval of weak (either recently learned or arbitrary) associations between symbols and possible actions. Our other findings cannot be explained by an effect of arbitrariness.

Discussion

The post-scan tests confirmed that subjects knew the meaning of a majority of the Old and Trained signs but very few of the Untrained signs. Therefore, we had sufficient trials to compare brain activation associated with viewing of three types of stimuli: (1) signs that subjects had known and used while driving for at least 4 years (correct Old), (2) signs that they had learned the meaning of prior to scanning (correct Trained), and (3) signs that they had viewed prior to scanning but did not know the meaning of (incorrect, a majority of which were Untrained). A comparison

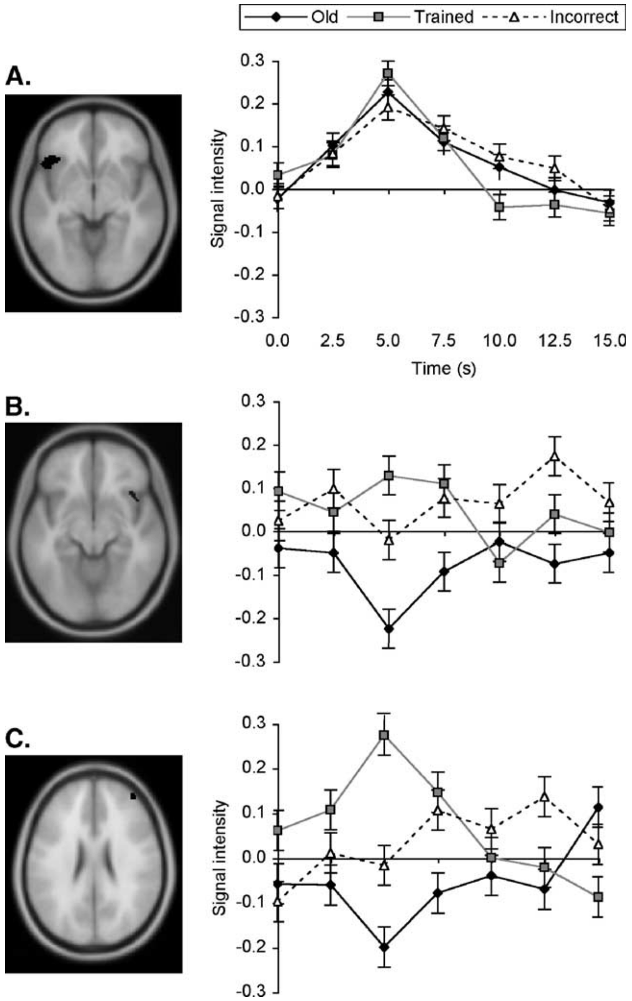

Fig. 4. ROI analyses for PFC subregions. (A) ROI in left VLPFC (BA 45; −52, 26, 2) obtained from the whole-brain contrast of all conditions > fixation. (B) ROI in right VLPFC (BA 47/11; 34, 24, −14) identified from the Trained > Old contrast. (C) ROI in right DLPFC (BA 9/10; 40, 50, 26) identified from the Trained > Old contrast. The corresponding time-series data are shown to the right of each ROI. These plots show that left VLPFC is engaged across conditions, whereas right VLPFC and DLPFC are most strongly engaged by the Trained signs. Error bars depict an estimate of the within-subject standard error.

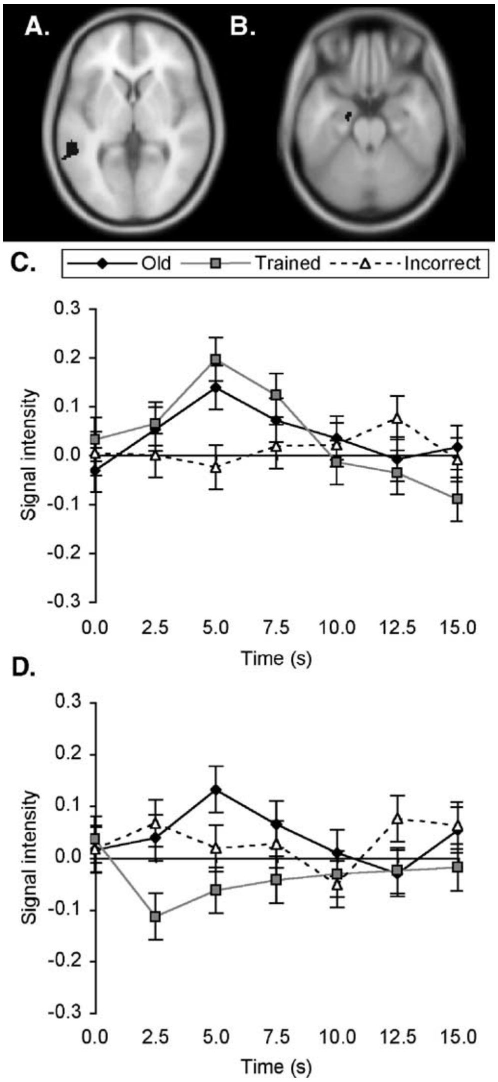

Fig. 5. ROI analyses are shown for regions in left lateral temporal cortex and MTL identified from the whole-brain contrast of correct > incorrect trials ($P < .001$). (A) Left postMTG (BA 21; −56, −40, 2). (B) Left MTL (−20, −10, −24). Time-series data are plotted for (C) left postMTG and (D) left MTL. These plots reveal knowledge-related modulation in postMTG (correct > incorrect) but experience-related modulation in the MTL (Old > Trained). Error bars depict an estimate of the within-subject standard error.

between correct and incorrect trials allowed us to test whether postMTG was modulated by rule knowledge. Furthermore, a comparison between correct Trained and correct Old trials allowed us to test whether VLPFC would be more strongly engaged when viewing signs whose meaning did not come to mind as automatically (Trained > Old). The comparison of Trained and Old trials is a stringent test of the controlled retrieval hypothesis of VLPFC function because differences in accuracy, RTs, and confidence judgments[1] between these conditions were slight (see also Demb et al., 1995), especially in comparison to the differences in level of experience.

Temporal lobes

Based on our prior study involving recently learned task rules, we had hypothesized that knowledge of actions associated with visual cues would be represented in postMTG (Bunge et al., 2003; see also Bunge, 2004). The present study supports this hypothesis by showing that left postMTG was more active when subjects passively viewed signs for which they knew the meaning than for signs that were familiar but not meaningful to them (correct > incorrect). Other activations in lateral temporal cortex were also identified by this contrast, but the largest and most significant focus was in the predicted region of left postMTG.

In contrast to the finding that left postMTG and other temporal cortical foci were modulated by knowledge, these regions were insensitive to level of experience (correct Old vs. Trained). This pattern of greater activation for meaningful signs, regardless of how automatically meaning is likely to be retrieved, is consistent with two hypotheses: first, that activation of the correct representation in temporal cortex contributes to remembering the sign's meaning, and second, that these temporal cortex representations can be activated either through effortful, top–down processes involving VLPFC or through automatic, bottom–up means.

In the semantic memory literature, a similar region in postMTG has been characterized as representing knowledge about actions associated with manipulable objects, such as tools (Beauchamp et al., 2002; Chao et al., 1999; Martin and Chao, 2001; Martin et al., 1996). PostMTG is active when subjects perform tasks requiring them to retrieve actions associated with objects (for a review, see Johnson-Frey, 2004). However, this region is also engaged when subjects simply view or name objects (Kellenbach et al., 2003; Mummery et al., 1996) . In fact, postMTG activation has been shown not to depend on whether or not the task *requires* retrieval of action-related knowledge but rather on whether the object being viewed can be easily manipulated (e.g., a hammer) or not (e.g., a park bench) (Kellenbach et al., 2003). These findings have been taken as evidence that postMTG activation reflects the automatic retrieval of action and motion representations associated with manipulable objects (Kellenbach et al., 2003). PostMTG activation is not specifically associated with knowledge about objects; indeed, it is also active when subjects view pictures of animals with which we have associated specific actions (Tyler et al., 2003). This body of evidence suggests that postMTG is involved whenever subjects either explicitly or implicitly retrieve functional knowledge about an object or entity.

A comparison of activation foci confirmed that the left postMTG activations from the present study and our prior rule study (Bunge et al., 2003) are close to, and in some cases overlapping with, foci from these studies on action knowledge (Bunge, 2004). The tool action foci tended to extend more posteriorly than the rule foci[2], although it is currently unclear whether this difference is real or artifactual (e.g., due to methodological differences, the use of different subject pools, or the fact that fewer rule studies were available for inclusion in the analysis). Ongoing research in the laboratory is focused on testing a single group of subjects on several paradigms to determine (1) whether the same region of postMTG stores rules and other action-related knowledge and (2) whether postMTG is active when

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[1] Indeed, subjects tended towards being more confident of their correct answers for Trained than Old trials, probably because they were explicitly told the meaning of the Trained but not Old signs prior to scanning.

[2] The y coordinate for action knowledge studies was on average around −50 mm. For the current study, the postMTG activation extended as far back as −52 mm, but the local maximum was at -46 mm.

subjects view cues that are meaningful but that are not associated with specific actions. Nonetheless, the present findings raise the intriguing possibility that postMTG plays a general role in storing action knowledge. This role may encompass both the representation of non-arbitrary associations between entities in the real world and specific actions, as well as of completely arbitrary associations between symbols and associated rules for how to act.

In contrast to lateral temporal cortex, the left MTL was more active for correct Old than for either correct Trained or incorrect trials. This finding is consistent with a large literature implicating the hippocampus in episodic memory retrieval (e.g., Eldridge et al., 2000; Manns et al., 2003; Vargha-Khadem et al., 1997). Subjects are expected to have stronger contextual associations for Old signs, which they have previously encountered in their daily life, than for new signs that they encoded for the first time immediately prior to scanning. In summary, whereas the postMTG activation profile reflects semantic memory for sign meanings, the preferential MTL activation for Old trials is likely to reflect the retrieval of episodic memory traces associated with these signs.

Lateral prefrontal cortex

By contrast to postMTG, PFC was not sensitive to rule knowledge. Right anterior VLPFC and DLPFC were more strongly engaged by Trained than Old correctly retrieved signs and incorrectly retrieved (primarily Untrained) signs. Thus, right VLPFC showed the predicted pattern of activation: greater involvement when subjects attempted to retrieve recently learned rule meanings relative to well-learned ones—and also relative to signs for which they had never been taught the meaning. This finding implicates right VLPFC in the effortful retrieval of sign meanings, consistent with predictions that we have previously made in the context of visual associative memory retrieval (Bunge et al., 2004). Our previous study had implicated right, but not left, VLPFC in the retrieval of non-verbal associations between meaningless visual stimuli. This prior finding, together with the known left/right hemispheric asymmetry in VLPFC for verbal and non-verbal materials (Kirchhoff et al., 2000; for review see Buckner et al., 1999; Wagner et al., 1999), leads us to hypothesize that right VLPFC retrieves non-verbal associations for the visual stimuli used in the present study.

In contrast to right VLPFC, left anterior and posterior VLPFC were consistently active during sign viewing, but their activation profiles did not reflect either rule knowledge or level of experience. Left VLPFC has been consistently implicated in the controlled retrieval of verbal associations (Badre and Wagner, 2002; Buckner et al., 1995; Fiez, 1997; Gabrieli et al., 1996, 1998; Petersen et al., 1988; Poldrack et al., 1999). However, the current study design did not include explicit task requirements but rather encouraged subjects to interpret each sign during the 5 s that it was shown on the screen. This open-ended task instruction may account for the fact that VLPFC was robustly but not differentially engaged across conditions. We have previously shown that left VLPFC is modulated by rule complexity during presentation of an instructional cue, which suggests that it is indeed involved in rule retrieval (Bunge et al., 2003). In the current study, signs assigned to the Trained and Untrained conditions were counterbalanced across subjects, so there should be no systematic difference in rule complexity between them. The current finding is consistent with the ‘left-brain as interpreter’ idea that left PFC is consistently engaged in an effort to derive meaning from the environment (Gazzaniga, 1985).

Although our predictions about PFC involvement in memory retrieval were focused on VLPFC, it is worth noting that right DLPFC (BA 8/9 and 9/10) also showed greater activation for Trained than either Old or incorrect signs. Neither region in DLPFC was functionally dissociable from right VLPFC in this study. Right DLPFC has been hypothesized to play a role in monitoring retrieval attempts and/or the products of retrieval (e.g., Rugg et al., 2003; Schacter et al., 1997). Several recent studies have suggested that *both* left and right PFC are involved in closely monitoring mnemonic content, but in different ways (Dobbins et al., 2004; Mitchell et al., 2004; see Ranganath, 2004). One of these studies (Dobbins et al., 2004) has characterized the left/right PFC distinction as relating to whether subjects base their memory judgments on specific contextual information (left PFC) or on item familiarity (right PFC). In a related vein, another study (Mitchell et al., 2004) posits that the laterality differences relate to whether subjects make memory judgments based on specific information relating to an item (e.g., its perceptual features) or on undifferentiated information (e.g., familiarity or recency of encoding).

Neither of these characterizations of right DLPFC contributions to memory, as currently formulated, can adequately account for the current data. First, subjects in our study were not required to make any memory judgments. Second, right DLPFC was observed for a contrast between Trained and Old signs for which subjects could later correctly explain the meaning—i.e., presumably during retrieval of specific information. Moreover, subjects were not more likely to confidently recollect Old signs (in fact, the trend was in the opposite direction), which does not fit with the hypothesis that right DLPFC is important when decisions must be made under situations of uncertainty (e.g., Henson et al., 2000). Rather, the current finding of activation for Trained relative to both Old and incorrect items fit with an account whereby right DLPFC (or at least, anterior BA 8/9 and 9/10) is associated with post-retrieval monitoring of information about items that do not have rich contextual associations.

Motor-related cortical regions

Like postMTG, neuroimaging studies of action knowledge have consistently reported activation in left ventral premotor cortex (PMv; BA 6/44) (for review see Johnson-Frey, 2004; Kellenbach et al., 2003). This region is active when subjects observe or copy movements, pretend to use tools, or generate verbs. As such, left PMv is thought to store movement representations and to support the retrieval of motor information about tool use (Kellenbach et al., 2003). In the current study, left PMv and pre-SMA were significantly more active for Trained than Old signs, but the profiles in these regions appeared as less marked inverted-U functions than those observed in right lateral PFC. Additionally, PMv was more active for signs rated as arbitrary than those rated as non-arbitrary, consistent with a role in controlled retrieval of actions associated with symbolic cues. Unlike temporal cortex, PMv and pre-SMA activation did not reflect rule knowledge, in that these regions were not more active for correct than incorrect signs. These results tentatively suggest that PMv and pre-SMA may have assisted in attempts to retrieve action knowledge, despite the fact that subjects were not required to carry out a motor response.

Another region that is sometimes reported in the action knowledge literature is posterior parietal cortex (in particular, the supramarginal gyrus and intraparietal sulcus; BA 40); (Johnson and Grafton, 2003; Johnson-Frey, 2004; Kellenbach et al., 2003). Left posterior parietal cortex appears to be recruited only when subjects retrieve specific actions (Kellenbach et al., 2003), such as grasp-related movements associated with tools (Chao and Martin, 2000). This finding is consistent with the literature on ideomotor apraxia indicating that patients with damage to this region have difficulty retrieving appropriate action representations (Heilman et al., 1997; see also Bunge et al., 2002). In the current study, some parietal activation was observed during sign viewing, but the foci were not close to those reported in the tool literature, and activation did not differ across conditions. In our prior rule study, the left inferior parietal lobule was sensitive to rule complexity during presentation of the instructional cue, as well as when subjects had to keep the rule in mind until they were prompted to select a response. In the current study, it is not surprising that parietal cortex was not implicated in rule knowledge retrieval, given that the signs were not associated with specific motoric actions, and that subjects were not required to make a response at any time during the scans.

Conclusion

To our knowledge, this constitutes the first study to explicitly examine where, *and in what form*, rules are stored in long-term memory. These results suggest that postMTG stores the meanings of arbitrary visual cues that specify actions, regardless of when these cues were originally learned or how much experience one has had with them. Moreover, these results implicate right VLPFC in controlled rule retrieval, even in the absence of explicit task demands. With these and other findings, significant headway is being made towards understanding how we retrieve and use rules to select an appropriate course of action (Brass and von Cramon, 2004; Bunge et al., 2003; Sakai and Passingham, 2003; for reviews see Bunge, 2004; Murray et al., 2000).

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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.2005.03.019.

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