*J Neurophysiol* 90: 3419–3428, 2003.
First published July 16, 2003; 10.1152/jn.00910.2002.

# Neural Circuits Subserving the Retrieval and Maintenance of Abstract Rules

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Submitted 11 October 2002; accepted in final form 2 July 2003

**Bunge, Silvia A., Itamar Kahn, Jonathan D. Wallis, Earl K. Miller, and Anthony D. Wagner.** Neural circuits subserving the retrieval and maintenance of abstract rules. *J Neurophysiol* 90: 3419–3428, 2003. First published July 16, 2003; 10.1152/jn.00910.2002. Behavior is often governed by abstract rules or instructions for behavior that can be abstracted from one context and applied to another. Prefrontal cortex (PFC) is thought to be important for representing rules, although the contributions of ventrolateral (VLPFC) and dorsolateral (DLPFC) regions remain under-specified. In the present study, event-related fMRI was used to examine abstract rule representation in humans. Prior to scanning, subjects learned to associate unfamiliar shapes and nonwords with particular rules. During each fMRI trial, presentation of one of these cues was followed by a delay and then by sample and probe stimuli. Match and non-match rules required subjects to indicate whether or not the sample and probe matched; go rules required subjects to make a response that was not contingent on the sample/probe relation. Left VLPFC, parietal cortex, and pre-SMA exhibited sensitivity to rule type during the cue and delay periods. Delay-period activation in these regions, but not DLPFC, was greater when subjects had to maintain response contingencies (match, non-match) relative to when the cue signaled a specific response (go). In contrast, left middle temporal cortex exhibited rule sensitivity during the cue but not delay period. These results support the hypothesis that VLPFC interacts with temporal cortex to retrieve semantic information associated with a cue and with parietal cortex to retrieve and maintain relevant response contingencies across delays. Future investigations of cross-regional interactions will enable full assessment of this account. Collectively, these results demonstrate that multiple, neurally separable processes are recruited during abstract rule representation.

## INTRODUCTION

Human behavior is frequently guided by rules or sets of constraints that guide performance by specifying how perception should be linked to action. Many rules that govern behavior are abstract in that they are not bound to a specific context or stimulus but rather can be retrieved and applied to familiar and novel situations alike (Wallis et al. 2001). Effective goal-directed behavior often requires the representation and implementation of the appropriate rule for a given context. The controlled implementation of rules is particularly important under situations in which automatic or overlearned responses are insufficient for successful task performance (Cohen et al. 1996; Miller and Cohen 2001). Although abstract rules play an important part in governing behavior, there is a limited understanding of how these behavior-guiding rules are represented in the brain.

Initial insights into the neural substrates of rule representation have emerged from neuropsychological, neurophysiological, and neuroimaging studies, each of which has implicated prefrontal cortex (PFC) as an important component of the circuitry underlying rule-based behavior. For example, patients with prefrontal damage have difficulty implementing contextually appropriate rules (Comalli et al. 1962; Luria 1966; Milner 1963), even when they are able to articulate the rules (Shallice and Burgess 1991). Lesion studies in non-human primates have confirmed the importance of PFC for rule-guided behavior (Parker and Gaffan 1998; Passingham 1993; Petrides 1985), and electrophysiological studies have shown that individual PFC neurons in non-human primates exhibit rule-sensitive activity (Asaad et al. 1998; White and Wise 1999). Moreover, neuroimaging data in humans indicate that activation in lateral PFC is associated with the active maintenance of contextual knowledge used to guide subsequent behavior (Braver et al. 2002; MacDonald et al. 2000; Sakai and Passingham 2003; for theoretical discussion, see Cohen and Servan-Schreiber 1992; O'Reilly et al. 2002).

Although evidence from neuropsychological, electrophysiological, and brain-imaging experiments converge on PFC as central to rule representation, what is less clear from these distinct lines of research is the contribution to rule representation of specific PFC subregions. According to one perspective, dorsolateral PFC (DLPFC) is important for representing and maintaining contextual information—including goals and rules—that guides behavior (e.g., Braver et al. 2002; Cohen and Servan-Schreiber 1992). For example, representation of context or rule information governing Stroop task performance has been observed to elicit DLPFC activation (e.g., Banich et al. 2000; MacDonald et al. 2000). Seemingly consistent with this perspective, Wallis et al. (2001) provided suggestive evidence that DLPFC may play a greater role in rule maintenance than does ventrolateral PFC (VLPFC). In that electrophysiological study, non-human primates were cued to follow a match-to-sample or non-match-to-sample rule, and neurons thought to be rule sensitive were defined as those preferring a particular rule irrespective of the stimulus cueing the rule. Wallis et al. (2001) noted that a higher proportion of DLPFC

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than VLPFC neurons exhibited rule selectivity during presentation the task cue and a sample stimulus. However, more recent in-depth analyses revealed no differences between VLPFC and DLPFC neurons in terms of latency or strength of rule selectivity at encoding, arguing against a functional dissociation between these PFC subregions (Wallis and Miller 2003; see also White and Wise 1999).

Seemingly at odds with the perspective emphasizing DLPFC involvement in rule representation are data from neuropsychological and neuroimaging studies involving conditional visuomotor tasks. In both humans and non-humans, VLPFC, rather than DLPFC, has been observed to play a predominant role in learning, maintaining, and implementing simple rules that govern behavior (i.e., stimulus-response associations; Passingham 1993; Passingham et al. 2000; Petrides 1985; Petrides and Milner 1982; Toni et al. 1998, 2001). Convergent with these observations, Bussey et al. (2002) reported that lesions of VLPFC in non-human primates disrupt the acquisition and expression of a match-to-sample rule that was similar to that adopted by Wallis et al. (2001).

In the present study, event-related functional MRI was used to examine the contributions of PFC subregions and posterior cortices to rule representation in humans. In particular, we sought to test whether DLPFC, VLPFC, or both would be implicated in retrieving and maintaining abstract rules similar to those examined in the study by Wallis et al. (2001). Building on their assertions, we defined regions that represent abstract rules as regions exhibiting sensitivity to rule complexity but insensitivity to the type of cue signaling the rule. Given the competing hypotheses regarding VLPFC and DLPFC involvement in rule-governed behavior, we sought to explicitly test whether one or both lateral PFC subregions would exhibit activation that was sensitive to rule complexity.

For a rule to be applicable under novel circumstances, it must be represented in a manner that can be abstracted from the specific circumstances under which the rule was first learned. However, the initial retrieval of a relevant rule is necessarily bound to the cue (i.e., the stimulus or set of circumstances) that elicits its retrieval. Thus one might expect the pattern of PFC activation to change over the course of rule-governed behavior, exhibiting sensitivity to cue type during the initial processing of an instructional cue but becoming cue-independent during a subsequent delay period that required rule maintenance. Such a finding would constitute evidence for abstract rule maintenance that depends on PFC.

On each trial of the experiment, subjects viewed either a verbal or a nonverbal stimulus that cued a particular rule. Cue presentation was followed by a long and variable delay period during which subjects could retrieve the associated rule and hold it on-line. After the delay, sample and probe stimuli were sequentially presented, and subjects made a rule-governed response. For match and non-match rules (here referred to as *compound rules* because they follow the form of if-and-if-then statements), it was necessary to maintain a set of response contingencies across the delay period. for Go rules (referred to as *simple rules* because they follow the form of if-then statements), the cue signaled a specific response. The purpose of separating the cue and sample stimulus in time, rather than having them appear simultaneously as has been done previously (Wallis et al. 2001), was to identify rule-sensitive delay-period fMRI activation that was independent of sample stimulus processing or expectancy regarding the nature of the probe stimulus.

The study was designed to examine computations associated with rule retrieval and maintenance, and therefore we were particularly interested in brain activation associated with the cue and delay periods of each trial. We predicted that the processes subserving rule representations would differ between the cue and delay periods. Specifically, we posited that activation associated with the initial retrieval of cue-rule associations would be sensitive to cue type and rule type, whereas activation associated with the maintenance of abstract rules across the delay would be sensitive to rule type but insensitive to cue type.

## METHODS

### *Subjects*

Fourteen right-handed native-English-speaking volunteers (9 females; 18–23 yrs of age) received a $50 remuneration for participating. Data from two additional subjects were excluded due to equipment malfunction. Informed consent was obtained in a manner approved by the Human Studies Committee of the Massachusetts General Hospital and the Committee on the Use of Humans as Experimental Subjects at MIT.

### *Behavioral paradigm*

Prior to scanning, subjects learned to associate each of four verbal cues and each of four nonverbal cues with one of four rules: match, non-match, go left or go right (Fig. 1*A*). None of the cues had

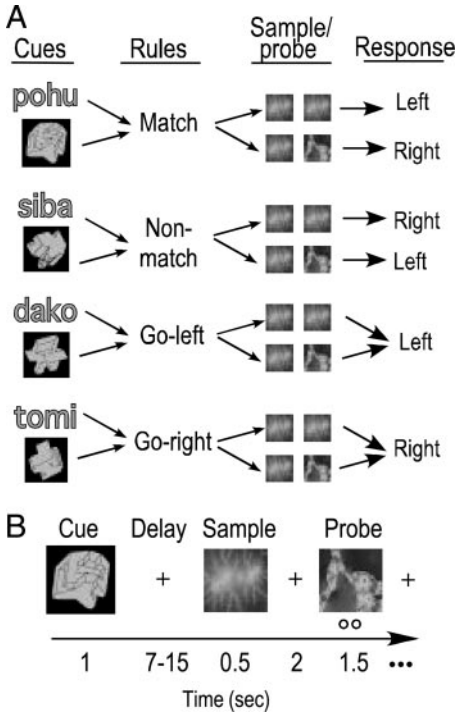


FIG. 1. Task. *A*: prior to the start of the experiment, subjects learned to associate each of 4 verbal and visual cues with a specific rule for behavior. Depicted here is an example of the rule label and relevant response contingencies associated with each cue. Specific cue-rule associations were counterbalanced across subjects. *B*: shown here is the timing of individual trials, which included a variable delay period of 7–15 s. Note: Fractals appeared in color in the experiment.

preexperimental associations: the verbal cues were pronounceable nonwords (e.g., "pohu"), and the nonverbal cues were unfamiliar shapes (impossible objects by P. Williams; http://www.cog.brown.edu/~tarr/stimuli.html#pw). Across 96 practice trials (12 trials per cue), subjects practiced naming the appropriate rule when presented a given cue. Additional trials were provided as needed until subjects could name all rules quickly and accurately.

After training on the cue-rule mappings, subjects were given an opportunity to practice the experimental tasks and then advanced to fMRI scanning. For each experimental trial (Fig. 1*B*), a cue was presented for 1 s, followed by a variable delay (ranging from 7 to 15 s in increments of 2 s). Subsequent to the delay, a picture was presented (the sample) and was followed by a second picture (the probe) that was either identical to or different from the sample. The sample and probe stimuli were colored fractals drawn from a set of four stimuli that were used throughout the experiment. Two white circles appeared below the second picture, indicating that the subject should make a response by pressing one of two buttons with their left hand. On match trials, subjects were to press the left button if the probe matched the sample and the right button if it did not match. On non-match trials, subjects were to press the left button if the probe did not match the sample and the right button if it matched. On go trials, subjects were to press either the left or right button depending on the cue (go left or go right), regardless of whether the probe matched the sample.

### *Data acquisition*

Subjects performed 180 experimental trials (60 match, 60 non-match, and 60 go trials) over the course of three fMRI scans. Visual stimuli were projected onto a screen that was viewed through a mirror. During each scan, subjects encountered eight cue/rule combinations (verbal and visual cues $\times$ match, non-match, go left, and go right rules). For each rule type (match, non-match, and go), there was an equal number of trials requiring a left-button and a right-button response. The order of trial types within each scan was determined using an optimal sequencing program designed to maximize the efficiency of recovery of the BOLD response (Dale 1999). Periods of visual fixation lasting between 2 and 28 s, jittered in increments of 2 s, were interleaved with the experimental trials as determined by the optimization algorithm. Owing to the variable delay, the design ensured that the regressors of greatest interest (cue and delay periods) were uncorrelated (max $r = -0.05$). The delay and sample/probe period regressors were only modestly correlated (max $r = 0.3$).

Scanning was performed on a 1.5 T Siemens system using a standard whole-head coil. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2 s, TE = 40 ms, 21 axial slices, 3.125 $\times$ 3.125 $\times$ 5 mm, 1-mm inter-slice gap, 650 volumes per run). Prior to each scan, four volumes were discarded to allow for T1-equilibration effects. High-resolution T1-weighted (MP-RAGE) anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head.

### *fMRI data analysis*

Data were preprocessed using SPM99 (Wellcome Dept. of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction (using sinc interpolation). Structural and functional volumes were spatially normalized to T1 and EPI templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco et al. 1997), an approximation of Talairach space (Talairach and Tourneaux 1988). Functional volumes were spatially smoothed with an 8-mm FWHM isotropic Gaussian kernel.

Statistical analyses were performed using the general linear model in SPM99. The fMRI time series data were modeled by a series of epochs and events convolved with a canonical hemodynamic response function. The cue period of each correct trial was modeled as an event, the delay period as a variable-duration epoch, and the period consisting of the sample and probe as a fixed-duration 4-s epoch. Error trials, which were few in number, were modeled with a variable-duration epoch spanning all trial periods and were considered covariates of no interest. 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 and a covariate for session effects. The least-squares parameter estimates of height of the best-fitting synthetic HRF for each condition were used in pairwise contrasts, and the resulting contrast images computed on a subject-by-subject basis were submitted to group analyses. 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 five contiguous voxels that exceeded an uncorrected threshold of $P < 0.001$.

Region-of-interest (ROI) analyses were performed to further characterize—in an unbiased manner—the rule and cue sensitivity of frontal, temporal, and parietal regions that were considered candidates for subserving rule retrieval, representation, and maintenance. Averaging the signal across voxels, as is done in ROI analyses, captures the central tendency and tends to reduce uncorrelated variance. Thus ROI analyses have greater power than whole-brain statistical contrasts to detect effects that are present across a set of voxels (Buckner et al. 1998). Unless otherwise noted, each ROI included all significant voxels ($P < 0.001$) within a 6-mm radius of each maximum defined from the contrast of delay period activation relative to the fixation baseline, averaging across rule and cue types. This standard ROI procedure identifies voxels engaged by the task without biasing the results in favor of observing differences between conditions. This approach does introduce the possibility that regions sensitive to a subset of the conditions might go undetected. However, as discussed in the following text, the a priori regions of interest in prefrontal, temporal, and parietal cortices were identified by this approach. Signal within an ROI was calculated for each subject by selectively averaging the data with respect to peristimulus time for trials in each condition. Statistics were performed on the peak amplitude of response associated with each condition during the cue and delay periods of the trial. The peak response during the cue period corresponded to 2- to 8-s postcue onset, and the peak during the delay period corresponded to 6- to 10-s postdelay onset. For all ROI analyses, effects were considered significant at an alpha of 0.05.

## RESULTS

### *Behavioral data*

Accuracy and speed of responding varied across rule type but not cue type (alpha threshold of 0.05). Specifically, analyses of variance with rule (go, match, non-match) and cue type (visual, verbal) as factors revealed significant effects of rule type on performance [accuracy: $F(2,26) = 5.2$; reaction time (RT): $F = 47.9$; Fig. 2]. Accuracy did not differ between go and match trials [$F(1,13) = 1.4$] but was superior for go than for non-match trials [$F = 10.1$]. RTs declined from non-match to match [$F(1,13) = 9.5$] to go trials ($F = 42.2$). Cue type (visual, verbal) did not reliably affect performance [accuracy: $F(1,13) = 1.5$; RT: $F < 1.0$], and the rule $\times$ cue type interactions were not significant [accuracy: $F(2,26) = 1.8$; RT: $F < 1.0$]. To minimize differences in brain activation related to differences in accuracy, all fMRI analyses were restricted to trials on which performance was accurate.

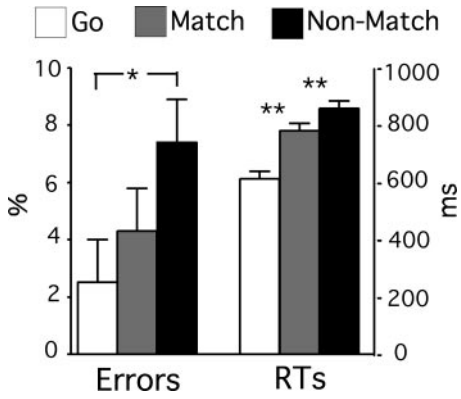


FIG. 2. Behavioral performance. Accuracy and reaction times (RTs) during task performance are displayed separately for go, match, and non-match rules. In all figures, error bars depict within-subject SE. *$P < 0.005$; **$P < 0.0001$.

### *Task-related activations*

As a first step in the fMRI data analysis, we averaged across conditions to identify regions that were activated during cue presentation or during the subsequent delay period (Fig. 3). The cue-period contrast identified regions engaged while subjects retrieved the rule associated with a cue, whereas the delay-period contrast identified regions engaged while rules were maintained across a delay.

Cue-period activations were observed in multiple cortical and subcortical structures, including bilateral primary and secondary visual cortices [~Brodmann's area (BA) 17/18], precuneus (~BA 19), superior and inferior parietal (~BA 7/39/40), posterior temporal (~BA 22/37/38), and anterior and posterior cingulate cortices (~BA 24/29/31) as well as bilateral parahippocampal cortex, basal ganglia (left caudate, bilateral putamen, right globus pallidus), and thalamus. Frontal lobe activations included bilateral premotor cortices, left presupplementary motor area (pre-SMA), right motor cortex, bilateral VLPFC (~BA 44/45/47), left DLPFC (~BA 9/46), and frontopolar cortex (FPC; ~BA 10). Delay-period activation was observed in many of the same regions that were active during the cue period, including robust responses in bilateral PFC and parietal and temporal cortices (Fig. 3). Thus these initial analyses demonstrated robust activation in a widely distributed set of regions during both cue and delay periods. Subsequent analyses focused on characterizing the sensitivity of a priori expected regions—prefrontal, parietal, and temporal cortices—to cue type and rule complexity.

### *Cue sensitivity*

Regions exhibiting sensitivity to cue type (verbal vs. visual) presumably contributed to the processing of the cue stimulus and/or to the retrieval of the rule associated with the cue. Among the regions of interest, bilateral VLPFC, right FPC/DLPFC, bilateral parietal cortex, and left parahippocampal cortex were more responsive to visual (shape) than verbal (nonword) cues during the cue period (Table 1). In contrast, only one region, in left middle temporal cortex (–54 –39 3; ~BA 21/22), was more responsive to verbal than visual cues during cue presentation. Finally, although a number of the regions of interest were sensitive to cue type during the cue period, only left premotor cortex showed an effect of cue type during the delay period (Table 1).

### *Regions involved in abstract rule maintenance*

The aim of the present study was to explore how PFC contributes to abstract rule representation and maintenance, including determining the relative roles of VLPFC and DLPFC in rule-governed behavior. Regions were considered to be involved in abstract rule maintenance if they met the following criteria: delay-period activation, sensitivity to rule complexity during the delay period, and insensitivity to cue type during the delay period. As just discussed, the PFC, temporal, and parietal regions of interest were insensitive to cue type during the delay period. Accordingly, we next turned our attention to determining whether any of these regions—which were defined as showing reliable delay-period activity—were sensitive to rule complexity.

ROI analyses revealed a number of regions that were sensitive to rule type during the delay (non-match, match, go; Table 1). Specifically, regions in left posterior VLPFC, FPC, pre-SMA, and superior and inferior parietal cortices exhibited rule sensitivity *without* cue sensitivity during the delay period (Table 1, Fig. 4). As is clear from Fig. 4, VLPFC and parietal cortical sensitivity to rule complexity generalized across the two compound rules, whereas FPC was particularly sensitive to the non-match rule, a point to which we return in the following text. Critically, in contrast to VLPFC and FPC, the bilateral DLPFC regions (~BA 46/9) observed to be active during the delay period were insensitive to rule type during this delay (Table 1; Fig. 5).

Many of the regions sensitive to rule type during delay, as well as other regions that were insensitive to rule type during delay, showed an effect of rule type during the cue period (Table 1). Specifically, left anterior VLPFC (~BA 47), posterior DLPFC (~BA 9; Fig. 5), and middle temporal cortex (~BA 21; Fig. 4) were sensitive to rule type during the cue period, but this rule sensitivity was not significant during the delay (anterior VLPFC and middle temporal cortex: $P > 0.40$; posterior DLPFC: $P = 0.13$). Thus the present data predominantly implicate VLPFC, rather than DLPFC, in rule retrieval and maintenance. Anterior and posterior VLPFC were both engaged during the retrieval stage with posterior VLPFC computations continuing to play a role during the maintenance period.

In the posterior VLPFC and parietal ROIs that exhibited rule sensitivity across the cue and delay periods, the nature of rule

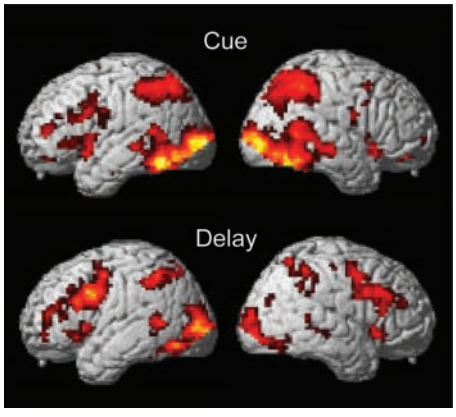


FIG. 3. Rendered here on canonical brains are the results of group analyses identifying regions engaged during the cue and delay periods of task performance relative to fixation ($P < 0.001$).

TABLE 1. *Cue and rule sensitivity analysis in frontal, parietal, and temporal ROIs defined as showing delay-period activity*

| Region of Activation | ~BA | Coordinates | | | Cue Type* (Visual > Verbal) | | Rule Type*† (Compound > Simple) | |
|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | Cue | Delay | Cue | Delay |
| VLPFC | | | | | | | | |
| L Inferior Frontal (Fig. 4) | 44 | −42 | 6 | 30 | — | — | 0.007 | **0.01** |
| L Inferior Frontal | 44 | −45 | 18 | 24 | — | — | 0.003 | **0.009** |
| L Inferior Frontal | 47 | −30 | 21 | −6 | .02 | — | — | — |
| L Inferior Frontal | 47 | −36 | 33 | 0 | — | — | 0.005 | — |
| L Insula | 13 | −33 | 18 | 3 | .01 | — | — | — |
| R Inferior/Middle Frontal | 44/9 | 48 | 12 | 33 | .05 | — | 0.04 | — |
| R Inferior Frontal | 47/13 | 42 | 21 | −6 | .05 | — | — | — |
| DLPFC | | | | | | | | |
| L Middle Frontal (Fig. 5) | 9 | −51 | 12 | 36 | — | — | 0.006 | — |
| L Middle Frontal | 9 | −33 | 33 | 30 | — | — | — | — |
| L Middle Frontal | 9/46 | −36 | 39 | 27 | — | — | — | — |
| R Middle Frontal (Fig. 5) | 9 | 42 | 33 | 30 | — | — | — | — |
| Frontopolar | | | | | | | | |
| L Middle Frontal (Fig. 4) | 10 | −36 | 48 | 12 | — | — | 0.02 | 0.009 |
| R Middle Frontal | 9/10 | 36 | 45 | 24 | .01 | — | — | — |
| Premotor | | | | | | | | |
| L Medial Superior Frontal | 8 | −3 | 24 | 48 | — | 0.05 | 0.03 | **0.03** |
| L pre-SMA | 6 | −6 | 24 | 54 | — | — | 0.05 | **0.04** |
| Parietal | | | | | | | | |
| L Inferior Parietal (Fig. 4) | 40 | −36 | −51 | 45 | .007 | — | 0.02 | **0.0002** |
| L Superior Parietal | 7 | −24 | −57 | 45 | .04 | — | 0.02 | **0.01** |
| R Inferior Parietal | 40 | 36 | −51 | 48 | .02 | — | — | — |
| R Precuneus | 7 | 12 | −72 | 45 | .001 | — | — | — |
| Temporal | | | | | | | | |
| L Middle Temporal (Fig. 4) | 21 | −54 | −54 | 9 | — | — | — | — |
| L Middle Temporal | 21 | −63 | −48 | −3 | — | — | 0.02 | — |
| L Parahippocampal | 30 | −15 | −39 | −3 | .02 | — | — | — |

~BA, approximate Brodmann's area; L, left; R, right; ROI, region of interest; VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral PFC; *$P > 0.05$ not reported; †Bold text, compound > simple; plain text, other patterns of rule sensitivity.

representation changed across these two task periods. Specifically, during the cue period, activation was greater for non-match trials than either match or go trials but did not differ between match and go trials (NM > M, go). In contrast, during the delay period, activation was greater for compound than simple trials (NM, M > go; Fig. 4). This pattern suggests that these regions initially played a differential role in retrieving knowledge about non-match rules but then were engaged whenever subjects had to maintain multiple response contingencies across a delay—i.e., maintenance of either of the two compound rules.

### *Prefrontal, parietal, and temporal contributions to rule representation*

A question of central interest is whether the left VLPFC, parietal, temporal, and posterior DLPFC regions that were sensitive to rule type at either (or both) the cue and delay period (Figs. 4 and 5) play similar or distinct roles during rule-based behavior. The preceding analyses suggest that functional differences may be present across these ROIs, but evidence for such a difference requires a direct test between regions. Accordingly, to compare the response patterns across these ROIs during the cue and the delay periods, ANOVAs were performed on pairs of regions, with ROI, rule type (go, match, non-match), and cue type (visual, verbal) as within-subjects factors.

During the cue period, all four ROIs exhibited rule sensitivity such that the pattern of cue-period activations did not differ across region (interaction $P > 0.3$ for all pairs of ROIs). By contrast, as noted in the preceding text, only left posterior VLPFC and parietal cortex continued to exhibit rule sensitivity during the delay period. Between-region ANOVAs confirmed that the effects of rule type and cue type were similar in posterior VLPFC and parietal regions. Importantly, both regions showed a greater response during complex than during simple rules, although there was a trend ($P = 0.06$) for the effect of rule type to be greater in parietal cortex owing to a greater difference between complex and simple rules in this region. We then compared the pattern of posterior VLPFC activation with that in DLPFC and in temporal cortex. Critically, these direct comparisons confirmed that VLPFC rule sensitivity differed from that in DLPFC and temporal cortex during the delay period [ROI × rule type: $F(2,26) = 3.6$ and 3.5, respectively], reflecting the fact that only VLPFC showed a greater response during maintenance of both complex rules.

In summary, left posterior and anterior VLPFC, posterior DLPFC, parietal, and temporal cortices were sensitive to rule type during cue presentation, implicating these regions in rule retrieval. This rule sensitivity was sustained during the delay period in posterior VLPFC and parietal cortices, which suggests that these regions contribute to the active maintenance of the relevant response contingencies until a response can be made. In contrast, anterior VLPFC, posterior DLPFC, and temporal cortex did not exhibit rule-sensitive delay-period activity, which suggests that these regions do not support rule maintenance.

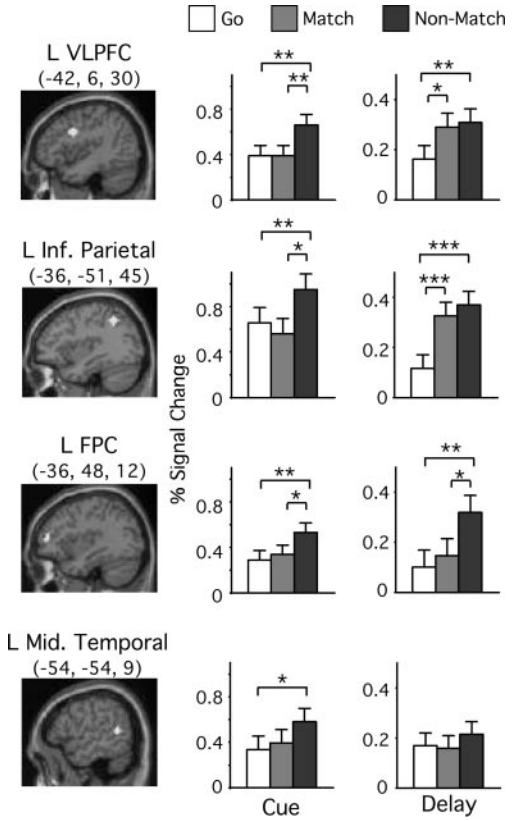


FIG. 4. Rule sensitivity of prefrontal, parietal, and temporal regions of interest (ROIs). Shown here are regions in left posterior ventrolateral prefrontal cortex (VLPFC), inferior parietal cortex, frontopolar cortex (FPC), and left middle temporal cortex that were rule-sensitive during the delay period (and the cue period). ROIs are plotted on canonical anatomical images. Graphs represent the integrated peak amplitude of response for ROIs across go, match, and non-match trials. ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$. Note: FPC ROI was identified from map-wise comparison at $P < 0.005$.

### *Dissociations between prefrontal subregions*

To further explore functional differences between VLPFC and DLPFC, we compared delay-period rule sensitivity between bilateral mid-DLPFC and left posterior VLPFC. Direct comparisons confirmed the presence of a ROI × rule type interaction between left posterior VLPFC and right mid-DLPFC [$F(2,26) = 9.6$, $P < 0.0008$]; the interaction between left posterior VLPFC and left mid-DLPFC did not reach significance [$F(2,26) = 2.3$, $P = 0.12$]. However, as noted in the preceding text, neither left nor right mid-DLPFC exhibited significant rule sensitivity (Table 1; Fig. 5). Thus the present data differentially implicate VLPFC, rather than either mid- or posterior DLPFC, in rule maintenance.

In comparison with posterior VLPFC, FPC exhibited a qualitatively different pattern of rule sensitivity during the delay period (Fig. 4). To assess whether these differences were reliable, a comparison between left posterior VLPFC and FPC (ROI × rule type × cue type) was performed. Although the ROI × rule type interaction did not reach significance [$F(2,26) = 1.8$], nevertheless, post hoc comparisons suggested that VLPFC and FPC exhibited different activation profiles for the compound rules during the delay period. Specifically, FPC was differentially sensitive to non-match trials relative to match and go trials [NM vs. M: $F(1,13) = 8.8$; M vs. go: $F < 1$], whereas VLPFC exhibited a pattern of greater activation for both compound rules relative to simple rules [NM vs. M: $F < 1$; M vs. go; $F(1,13) = 4.9$; Fig. 4]. Thus consistent with the preceding analyses, left VLPFC was associated with representing and maintaining compound rules. By contrast, left FPC was differentially sensitive to the non-match rule during both the cue and delay periods.

### *Task switching*

Although the focus of the present study was on understanding the neural correlates of abstract rule representation, the experiment also could be considered a task-switching experiment, in that subjects alternated between applying several different rules in a pseudorandom manner. Accordingly, we examined whether the brain regions implicated in rule representation were sensitive to task-switches. To do so, we coded each trial as a "non-switch" or "switch" trial, depending on whether subjects performed the same task (i.e., match, non-match, go left, or go right) as on the preceding trial. Cue-period activation for switch trials was compared with that for non-switch trials.

No region exceeded a statistical threshold of $P < 0.001$ uncorrected for the comparison of switch to non-switch trials. However, greater activation on switch than non-switch trials was observed at $P < 0.005$ uncorrected in bilateral anterior cingulate cortices (~BA 32; foci at –3 27 33; 12 24 33), right medial frontal cortex (~BA 8; 12 18 45), caudate nucleus (24 6 21), anterior insula (~BA 13; 39 21 3), and left inferior parietal lobule (~BA 40; –57 –33 33). When the threshold was further lowered to $P < 0.05$ uncorrected, activation also was revealed in right VLPFC (~BA 45; 39 21 3) and bilateral DLPFC (left ~BA 9; –24 45 30; right ~BA 9/8; 30 39 33). Critically, even at this liberal threshold, the regions activated by task switching did not overlap with those shown to be rule sensitive (i.e., rule-sensitive regions were not differentially engaged by switch and non-switch trials). This analysis indicates that the rule sensitivity observed in the present study was not related to task-switch demands.

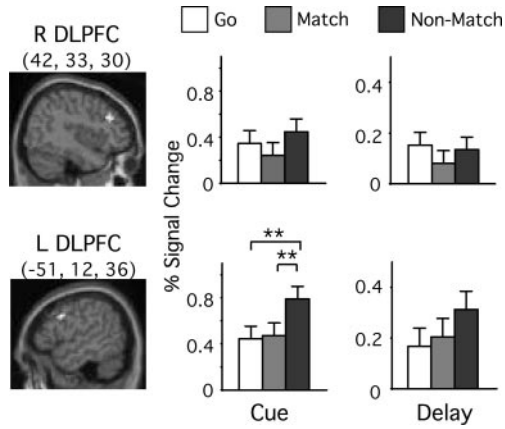


FIG. 5. Shown here are regions in right mid-DLPFC and left posterior DLPFC that did not exhibit a significant effect of rule type during the delay period ($P > 0.10$ for both ROIs), although the posterior DLPFC region was sensitive to rule type during the cue period. ROIs are plotted on canonical anatomical images. Graphs represent the integrated peak amplitude of response for ROIs across go, match, and non-match trials. **$P < 0.01$.

## DISCUSSION

The present study aimed to specify the neural correlates of rule retrieval and maintenance. The resulting data suggest that multiple, neurally separable processes are recruited during rule-based processing, differentially implicating VLPFC, rather than DLPFC, in the retrieval and maintenance of rule representations. The observed patterns of cue-period and delay-period activation are consistent with the following functional account. During cue presentation, mechanisms supported by left anterior and posterior VLPFC serve to guide retrieval of associated semantic (rule) information that may be represented in left temporal cortex. Subsequent to this retrieval, when abstract rules must be maintained across a delay period, the relevant response contingencies are actively maintained through interactions between posterior VLPFC and parietal cortex, enabling selection of the correct response at the end of the trial. Although these hypothesized across-region functional interactions warrant further assessment with a brain monitoring technique affording high temporal resolution or with cross-regional interaction analyses, the present findings nevertheless indicate that rule retrieval and maintenance, in humans, depend on multiple functional neurobiological processes, placing differential demands on VLPFC rather than DLPFC.

### *Cue- and delay-period representations*

The activation profiles in many regions—including prefrontal, parietal and temporal cortices—differed between the cue and delay periods (Table 1). A number of regions were sensitive to cue type during cue presentation but not during the delay. This finding suggests that cue-rule associations were retrieved in response to cue presentation, whereas stimulus-independent response contingencies were maintained during the delay. Moreover, while rule sensitivity was observed during cue presentation in a number of regions, the predicted pattern of sensitivity to compound relative to simple rules (non-match and match $>$ go) did not emerge until the delay period. This pattern of results supports the expected outcome: that cue-period activation is dominated by retrieval of cue-rule associations and that delay-period activation is dominated by maintenance of response contingencies.

### *Temporal cortex: storage and retrieval of cue-rule associations*

Posterior middle temporal cortex demonstrated an activation profile consistent with a role in rule retrieval but not maintenance. A cluster within this region exhibited sensitivity to rule type during cue presentation, but neither this nor any other region in temporal cortex exhibited significant rule sensitivity during the delay period. Posterior temporal cortex has been shown to be important for generating action words in response to objects (Fiez et al. 1996; Martin et al. 1995) and retrieving knowledge about tools (Chao et al. 1999; Tranel et al. 1997) and is thus thought to represent functional information about objects (Martin and Chao 2001). In the present study, this region was engaged by verbal and visual cues that had no meaning prior to the experiment. Thus we suggest that posterior middle temporal cortex represents semantic information about cues that have come to be associated with specific actions, even when these associations are arbitrary. Left middle temporal cortex may store the long-term knowledge that constitutes each abstract rule representation and thus is engaged during their retrieval.

### *Prefrontal and parietal regions implicated in rule maintenance*

In contrast to middle temporal cortex, a largely left-lateralized set of regions—including posterior VLPFC, pre-SMA, and inferior and superior parietal cortices—exhibited a pattern of sustained activation across the delay period that was sensitive to compound relative to simple rules. These findings implicate VLPFC and parietal cortex in the maintenance of response contingencies associated with a visually presented cue stimulus. These results are complementary to electrophysiological data in non-human primates demonstrating that individual PFC neurons can represent specific rules, regardless of the type of cue used to bring the rule to mind (Wallis et al. 2001). The present data extend the findings of Wallis et al. (2001) by identifying a distributed network supporting rule representation in humans and by demonstrating functional heterogeneity within the human PFC with regard to rule representation.

### *Parietal cortex: representing response contingencies*

Left inferior parietal cortex was sensitive to cue type (visual $>$ verbal) during cue presentation and to rule type (compound $>$ simple) during the cue and delay periods. This outcome is consistent with previous observations that response representations in parietal cortex are activated when subjects are presented visual stimuli that have been previously associated with a response (Bunge et al. 2002; see also Andersen 1987; Deiber et al. 1997; Denny-Brown and Chambers 1966; Goodale and Milner 1992; Snyder et al. 2000). Moreover, the present data indicate that parietal involvement may not be limited to transient representation of cue-associated response contingencies but rather may also be modulated during active maintenance of these contingencies until an appropriate response can be selected and initiated.

### *Ventrolateral PFC: controlled retrieval and maintenance of rule representations*

Within lateral PFC, the region most strongly implicated in rule maintenance was left VLPFC. VLPFC has been implicated previously in the learning and retrieval of conditional visuomotor rules, in which—like the go trials in the present study—visual cues are associated with specific responses (Murray et al. 2000; Parker and Gaffan 1998; Passingham et al. 2000; Toni and Passingham 1999; Toni et al. 1999). The present findings, together with a recent lesion study in non-human primates (Bussey et al. 2002), differentially implicate VLPFC in the retrieval and maintenance of more complex rules in which the cue does not specify a particular response but rather a set of response contingencies.

It has been suggested that VLPFC is critically involved in the ability to associate visual cues with appropriate actions (Murray et al. 2000; Passingham and Toni 2001). However, several alternative hypotheses have been proposed (see Passingham and Toni 2001): VLPFC identifies visual cues but does not determine the appropriate course of action; VLPFC is

involved in learning visuomotor associations but is not involved in retrieving the appropriate response once the associations have been learned; or VLPFC is not critically involved in visuomotor performance, but lesions to this region impair performance because they disconnect premotor and inferior temporal cortices (but see Bussey et al. 2002). The present study revealed that VLPFC is engaged during the retrieval and maintenance of highly practiced rules for behavior and is sensitive to rule complexity. These observations support the claim that left VLPFC is indeed involved in associating visual cues with appropriate actions, mediating retrieval of those action contingencies when cued.

While the present and prior studies indicate that VLPFC is involved in retrieving and maintaining behavior-guiding rules (Murray et al. 2000; Toni et al. 1999) and in learning new rules (Asaad et al. 1998; Passingham et al. 2000; Toni et al. 2001), lesion studies in humans suggest that PFC is unlikely to be the long-term repository of well-learned rules. In fact, one of the hallmarks of prefrontal damage is the tendency to rely on stereotyped rules for behavior (Mesulam 2002). Additionally, patients with prefrontal damage are often able to articulate the appropriate rule even if they are unable to implement it (Shallice and Burgess 1991). These observations suggest that PFC is likely to be important for learning new rules and for retrieving and maintaining relevant rules.

In the present study, both left anterior and posterior VLPFC were modulated by rule complexity during cue presentation. Previous neuroimaging studies have shown that these two subregions of VLPFC are functionally dissociable, with anterior VLPFC being differentially implicated in semantic processing (e.g., Buckner et al. 1995; Fiez 1997; Poldrack et al. 1999; Wagner 1999), often being engaged together with left middle temporal cortex during conceptual retrieval (e.g., Petersen et al. 1988; Raichle et al. 1994; Wagner et al. 1998). The finding that left anterior VLPFC was rule-sensitive during cue presentation is consistent with the posited role of this region in retrieving semantic knowledge associated with a stimulus (Badre and Wagner 2002; Buckner et al. 1995; Fiez 1997; Gabrieli et al. 1996, 1998; Petersen et al. 1988). Moreover, these data extend prior observations by demonstrating that this anterior VLPFC region is engaged during retrieval of experimentally acquired conceptual (rule) knowledge that has come to be associated with initially meaningless nonwords and objects.

By contrast, left posterior VLPFC—the PFC subregion presently linked with rule maintenance—has been strongly implicated in verbal working memory (see Smith et al. 1998). Prior imaging studies indicate that this region is active when subjects maintain verbal information over delays even when this information is devoid of semantic content (Awh et al. 1996; Paulesu et al. 1993; Poldrack et al. 1999; Smith et al. 1998). The present findings suggest that rules may be maintained in a similar manner to other types of verbalizable information, perhaps not enjoying a special status relative to item-specific phonological representations that are actively maintained during performance of verbal working memory tasks. However, it should be noted that the left VLPFC delay-period activation observed for compound relative to simple rules is unlikely to be related to maintenance of the verbal label associated with a rule as the labels match and non-match are no more phonologically demanding than the labels go left and go right. Instead, this delay-period activation may reflect increased phonological demands associated with maintaining a set of response contingencies rather than a specific response plan.

### *Ventrolateral versus dorsolateral PFC*

Although posterior DLPFC exhibited rule sensitivity during cue presentation, in contrast to posterior VLPFC, neither posterior nor mid-DLPFC regions were differentially engaged by compound and simple rules during the delay period. These results implicate VLPFC, rather than DLPFC, in the active maintenance of response contingencies, consistent with lesion data showing that—whereas VLPFC lesions impair the ability to learn or maintain visuomotor associations (Murray et al. 2000)—DLPFC lesions cause little to no impairment on this task (e.g., Petrides and Milner 1982). However, the current results cannot rule out the possibility that DLPFC plays some role in rule maintenance in humans, and that match-, non-match-, and go-selective neurons are interspersed within DLPFC, similar to what has been observed in non-human primates (Wallis et al. 2001).

### *Rule representation in FPC*

Several aspects of the present results suggest that left FPC, in addition to left VLPFC, contributes to rule representation. First, FPC was rule sensitive during the cue and delay periods. Second, this region was insensitive to cue type during cue presentation, suggesting that it may operate on the retrieved rules rather than the cues associated with them. Third, although FPC and VLPFC were both preferentially engaged by the non-match rule during the cue period, FPC continued to exhibit this pattern during the delay period, whereas VLPFC delay-period activity was greater during both compound rules relative to simple rules. The behavioral results revealed that the non-match rule was the most difficult to retrieve, consistent with prior observations (Elliott and Dolan 1999). Moreover, according to self-reports, some subjects conceptualized the non-match rule as "the opposite of match." Thus retrieval of the non-match contingencies may have required greater elaboration of the retrieved rule than did the match or go conditions. These results are consistent with the possibility that once a learned rule has been retrieved, subjects recruit FPC to help elaborate on this rule to retrieve the relevant response contingencies and thereby more effectively guide behavior. This account, which remains to be empirically tested, is informed by prior results suggesting that FPC operates on the products of lateral PFC (Braver and Bongiolatti 2002; Christoff and Gabrieli 2002; Sakai and Passingham 2003; S. A. Bunge, D. Badre, and A. D. Wagner, unpublished data).

### *Consideration of attentional demands*

It could be argued that brain regions that were more strongly engaged for compound than simple rules were sensitive not to rule complexity but rather to differences in demand on visuospatial attention between conditions. According to this view, on match and non-match trials, subjects had to pay attention to the identity of the upcoming sample and probe stimuli for match and non-match trials, whereas on go trials, they merely had to monitor the presentation of the two stimuli to respond to the second stimulus. Further experiments are required to definitively rule out this interpretation. However, sustained visual

attention is typically associated with right rather than left prefrontal and parietal activations (Awh and Jonides 1998; Cabeza and Nyberg 2000; Pardo et al. 1991; Wagner 1999) and right VLPFC activation has been observed during associative recognition decisions on visual patterns similar to those used in the present experiment (Bunge et al. 2003). These prior findings argue against a visuospatial attentional account of the left-lateralized prefrontal and parietal activations observed for complex relative to simple rules.

Another possible interpretation is that our results were influenced by task-switch demands because subjects were instructed to switch between rules on a trial-by-trial basis. A comparison of switch and non-switch trials ruled out this alternative interpretation in that it revealed a different network of regions sensitive to task switching—including medial frontal cortex, ACC, and the right insula, regions that previously have been implicated in task switching (e.g., Dove et al. 2000; Konishi et al. 2001; Rushworth et al. 2002)—from the network implicated in rule retrieval and maintenance. These results demonstrate that rule-sensitive regions were engaged to a similar extent regardless of whether the task they were instructed to perform was the same as that on the preceding trial. We predict—in contrast—that regions involved in rule retrieval would be *less* active on trials in which the specific *cue* (rather than the rule) was repeated due to reduced retrieval demands. There were insufficient cue-repeat trials to test this prediction in the present study.

### *Conclusion*

The present results implicate a network of largely left-lateralized regions in retrieving and actively maintaining response contingencies for the purpose of preparing to respond to an upcoming stimulus. These results support a model whereby left anterior and posterior VLPFC interact with temporal cortices to retrieve the rule associated with a particular cue, FPC reformulates the rule into a form that can be used to guide behavior more specifically, and posterior VLPFC and parietal cortices interact to maintain the relevant response contingencies. Further support for these hypotheses could come from an examination of interactions between these brain regions during rule retrieval and maintenance. Moreover, in the present study, response contingencies were cued by specific visual stimuli in the environment. Further studies that build on the present findings may examine how environmental cues are considered in concert with contextual knowledge—including overarching goals, memories of similar situations, and feedback about our internal state—during the selection of an appropriate response.

We thank B. Burrows for assistance with data collection and analysis, R. Poldrack for contribution to the experimental design and analysis code, and L. Davachi and B. Gonsalves for comments on the manuscript.

## DISCLOSURES

This work was supported by the National Science Foundation (0133126), McKnight Endowment Fund for Neuroscience, and P. Newton.

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